

THE NATIONAL INSTITUTES OF HEALTH: A RE- VIEW OF ITS REFORMS, PRIORITIES, AND PROGRESS

HEARING BEFORE THE SUBCOMMITTEE ON HEALTH OF THE COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES ONE HUNDRED TWELFTH CONGRESS

SECOND SESSION

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THE NATIONAL INSTITUTES OF HEALTH: A REVIEW OF ITS REFORMS, PRIORITIES, AND PROGRESS

THURSDAY, JUNE 21, 2012

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 9:36 a.m., in room 2123 of the Rayburn House Office Building, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Shimkus, Myrick, Murphy, Blackburn, Gingrey, Latta, McMorris Rodgers, Lance, Cassidy, Guthrie, Bilbray, Barton, Pallone, Dingell, Towns, Schakowsky, Markey, and Waxman (ex officio).

Staff present: Sean Bonyun, Deputy Communications Director; Brenda Destro, Professional Staff Member, Health; Sean Hayes, Counsel, Oversight and Investigations; Debbie Keller, Press Secretary; Ryan Long, Chief Counsel, Health; Katie Novaria, Legislative Clerk; Andrew Powaleny, Deputy Press Secretary; Krista Rosenthal, Counsel to Chairman Emeritus; Heidi Stirrup, Health Policy Coordinator; Alex Yergin, Legislative Clerk; Alli Corr, Democratic Policy Analyst; Ruth Katz, Democratic Chief Public Health Counsel; Elizabeth Letter, Democratic Press Secretary; and Anne Morris Reid, Democratic Professional Staff Member.

Mr. PITTS. This subcommittee will come to order.

The Chair recognizes himself for 5 minutes for an opening statement.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Good morning. On behalf of the Subcommittee on Health, I would like to welcome Dr. Francis Collins. I, and I know many of my colleagues, have admired your work as a researcher on the important Genome Project and now in your leadership role at NIH.

Americans take great pride in the work of NIH, whose roots date back to 1887. During that time, NIH has been in the forefront of biomedical discoveries that have revolutionized the field of medicine, including deciphering the genetic code and finding treatments and cures for so many diseases. More than 80 Nobel Prizes have been awarded for NIH-supported research. This record clearly

shows that NIH is a premiere research institution and a great American achievement.

Since 1887 when it operated as a one-room laboratory, NIH is now a large system of 27 Institutes and Centers. With the passage of the NIH Reform Act of 2006, Congress addressed some of the downsides of that rapid growth in order to improve outcomes. I look forward to an update on the implementation of the Reform Act, especially the role of the Scientific Management Review Board and the Common Fund.

NCATS, the National Center for Advancing Translational Sciences, is a new institute at NIH designed to catalyze technology toward the diagnosis and treatment of disease. Even though this is the first year of its operation, I would to like learn about its progress and the funding of a pilot program which partners with pharmaceutical companies to resurrect older drugs for new therapeutic uses.

Finally, Americans expect us to spend their tax dollars wisely. It is therefore very important that we set good priorities. Faced with so many good causes, I would like to know how NIH identifies the highest priorities in biomedical research and then uses the review process to fund the best research.

[The prepared statement of Mr. Pitts follows:]

Opening Statement of the Honorable Joseph Pitts
Subcommittee on Health
Hearing on NIH
June 21, 2012

(As Prepared for Delivery)

On behalf of the Subcommittee on Health, I would like to welcome Dr. Francis Collins. I, and I know many of my colleagues, have admired your work as a researcher on the important genome project and now in your leadership role at NIH.

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Mr. PITTS. I would like to yield the rest of my time to the vice chairman of the Health Subcommittee, Dr. Burgess.

**OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. BURGESS. I thank the Chair for yielding, and Dr. Collins, welcome to our committee. Any time that we get to spend a few hours with one of the premier minds in research science in the United States of America, and indeed, the world, it is a good thing and it is a good thing for our committee to have you here.

Certainly, all of us on this committee understand the importance of medical research conducted at the National Institutes of Health. I just have to say, in reading over your testimony in preparation for today, the concept of a small, inexpensive, high-powered microscope that could attach to your iPhone to give you information about the safety of drinking water, all I have to say is, is there an app for that?

You guys are doing the research, will, with the aid of the private sector, lead the next great treatments of the next century. This committee's commitment to authorizing the funding for National Institutes of Health has allowed you to become one of the premiere government health research foundations in the world and certainly we should all be concerned that we maintain that forward thinking and that we do not lose our position as the world's premier leader in research.

We are obviously going to be looking to you to answer questions, some questions that are now, some that have been raised in the past—how are we doing, how are we doing with keeping the lines of communication open between you and the head of the Centers for Medicare and Medicaid Services, and of course, with the Food and Drug Administration interposed between the laboratory bench and the delivery system, how is that bottleneck being resolved. How are genomics changing the way that we identify and treat disease, and certainly, in regard to the National Institutes of Health Reform Act, which created a formal planning process, the mechanism to fund interdisciplinary research projects and a grant of more coordinating authority to the Director. Are you able to sharpen your focus on diseases and conditions that heretofore have been such formidable challenges to research, your community and of course the world at large.

I am particularly interested to hear about the gains that you have made with translational research at the National Institutes of Health. We need to know what research has been funded by you, by the Director's office, that allows the allocation of funds from national research institutes to centers to award grants for high-impact, cutting-edge medical research, the intramural or extramural activities that go on that fund not just research at NIH but also at institutions of higher learning in Congressional districts throughout the country.

We have got a lot to cover this morning, Mr. Chairman. I am going to yield back the balance of my time.

Mr. PITTS. The Chair thanks the gentleman, and the Chair now recognizes the ranking member of the subcommittee, Mr. Pallone, for 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Mr. Chairman.

As we continue to work our way out of the recession towards a thriving economy that offers economic opportunities to all Americans, we must out-innovate, out-educate and out-build the rest of the world.

NIH is the driving force behind the biomedical research that has advanced and continues to improve the health of Americans and strengthen the U.S. economy. Thanks in large part to NIH research, Americans are living longer, living healthier and suffering less from morbidity and mortality of countless diseases when compared to the past. Not only has the general health of the Nation improved, but these gains have added an estimated \$3.2 trillion annually to the U.S. economy since 1970.

NIH funds critical biomedical research in all 50 States and the District of Columbia. It remains the leader not only in the American biomedical industry but also serves as a significant and sustainable part of our economy.

Now, let me use New Jersey as an example. New Jersey is home to more than 2,000 biotechnology companies, institutes and research facilities. During fiscal year 2004 to 2009, NIH awarded \$198 million to New Jersey biological science companies and venture capital firms and invested an additional \$4.1 million in biomedical firms during this period.

NIH also spurs innovation. In fiscal year 2011 alone, 28 New Jersey businesses received NIH grants towards R&D technology with potential commercial applications and \$4.9 million was awarded to train the next generation of scientists. In my district alone, nearly \$115 million was awarded in grants to research institutions in fiscal year 2011, and this helped not only provide jobs to establish a rich biomedical environment for our current and future workforce but also helps support the Rutgers University Cell and DNA Repository, the largest university-based repository in the world that maintains samples for the study of aging, longevity, substance use, and neurological disorders, and the impact of the grants is not limited to universities. Between 2000 and 2010, 37 startups were formed based on Rutgers University research.

It is often said that government can support and advance initial research that is developed by the private sector. Declining or stagnant Federal funding for research and development has an impact on all our sectors of our workforce. It has been estimated that for every dollar of NIH funding, we generate \$2.10 in local economic growth. A report from United Medical released in May argued that public investment in biomedical research has a dual benefit. By establishing the biomedical foundation upon which industries can build, public funding also has a private rate of return of 30 percent and a public return of at least 37 percent. Extensive studies have shown consistently that public investment in health and biomedical research improves health outcomes, alleviates burdens of disease, bolsters the infrastructure for our workforce, and provides quality jobs in our communities and States.

Again, using New Jersey as an example, New Jersey has been ranked as one of the largest R&D employers in the United States with more than 211,000 jobs supported by health R&D including 50,000 direct jobs in health R&D. And the same report shows the economic impact in New Jersey is \$60 billion. Economic research shows that public R&D and private R&D are mutually beneficial. They complement each other, and one cannot be substituted for the other.

And we do need to be honest: these are difficult economic times. But while our circumstances are mirrored in the international arena, our counterparts in Europe and Asia are steadily increasing their investments for biomedical research despite limited resources because of the long-term impacts on their citizens' health and their economy. America's competitiveness and status as a global leader depends on our ability to innovate and support bright, creative minds, transforming discoveries into health benefits and a stable future.

So the government must be responsible for facilitating an environment where Americans can continue to innovate. If government abandons its role, we run the real risk of squandering too many opportunities. And this should serve as an important call to us that only makes our role all the more critical. Are we willing to allow dramatic cuts and decreases in funding to jeopardize our ability to fight cancer, infectious disease, chronic illness and the development of critical components of our workforce and industry. I think we have a responsibility to the future now more than ever by making wise investments that can lead to so many innovative discoveries, the reduction of disease and so much in direct and cascading economic benefits. That is the key to creating new, thriving industries that will produce millions of good jobs here at home and a better future for the next generation.

So Mr. Chairman, I think it is about priorities. Americans' quality of life and bolstering our economy should be our top priorities. Government can plant the seeds often with modest investments relative to long-term payoffs in new products, new discoveries, new jobs and economic growth, and greater funding and support for NIH addresses both these priorities and it is a way to keep the United States healthy, strong and competitive.

So thank you, Mr. Chairman. This is a very important hearing.

Mr. PITTS. The Chair thanks the gentleman and now recognize the chair emeritus of the full committee, Mr. Barton, for 5 minutes for an opening statement.

**OPENING STATEMENT OF HON. JOE BARTON, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. BARTON. Thank you, Chairman Pitts and Ranking Member Pallone. I want to thank also Mr. Waxman and Chairman Upton.

This is a hearing that is being done, I won't say primarily at my request but it is a hearing that I have asked this subcommittee to hold. I think everyone on the committee remembers that back in 2006 when I was chairman, we did pass the NIH reauthorization bill, the first major reauthorization of the National Institutes of Health in, I believe, 13 years or maybe even longer.

The NIH is the gold star for medical research in the world. Under Speaker Gingrich's leadership and subcommittee Chairman John Porter's leadership a number of years ago, we doubled the budget of NIH. Unfortunately, in the last few years, we have not been able to give NIH those sorts of additional resources but the reform NIH reauthorization bill did give extra flexibility to the NIH. It created what we call the Common Fund. It helped reorganize the NIH and has been implemented, I think, in a fairly effective fashion.

Today we are here to hear from the Director, the distinguished doctor, how that reauthorization is proceeding and also get his input on the things that perhaps need to be done and need to be done legislatively that haven't been done. We want to make sure that the NIH is productive. We want to make sure that it is effective. And to the extent that we can increase funding, we want to provide transparency so that the public knows how their money is being spent. We also want to increase the communication and collaboration within the NIH and to as large an extent possible eliminate duplicity and redundancy. We also want to encourage emerging scientific opportunities, and I know the Director is going to speak, probably at some length, on that.

The reauthorization bill from 2006 has expired. It is my hope that this hearing will lay the foundation to perhaps in this Congress, and if not in this Congress, in the next Congress, to do another reauthorization bill of the NIH.

I want to thank you, Dr. Collins, for your leadership at the NIH, also for your friendship and your cooperation with me and other members of this subcommittee and the full committee.

With that, Mr. Chairman, I can yield the balance of my time to someone else.

Mr. PITTS. Mr. Lance from New Jersey is seeking recognition.

Mr. BARTON. I would like to yield the balance of my time to the distinguished gentleman from New Jersey, Mr. Lance.

OPENING STATEMENT OF HON. LEONARD LANCE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. LANCE. Thank you, Mr. Chairman, and thank you for yielding, Mr. Chairman Emeritus.

Since the passage of the National Cancer Act of 1971, there has been significant progress in the understanding of cancer biology, risk factors, treatments and prognosis of many types of cancer. However, in the past 40 years, we have yet to see significant progress in the diagnosis and treatment of pancreatic cancer.

Pancreatic cancer is the fourth-leading cause of cancer deaths in the United States. It will take the lives of over 37,000 Americans this year, 74 percent of whom will die within a year of diagnosis. In fact, the 5-year survival rate for pancreatic cancer is 6 percent, the only major cancer that continues to have a 5-year survival rate in single digits and a number that has remained virtually unchanged for 40 years.

It is projected that the number of new pancreatic cancer cases will increase by 55 percent between 2010 and 2030. Despite these harrowing statistics, the National Cancer Institute does not have

a comprehensive and strategic plan to address the disease and is currently allocating little more than 2 percent of its research budget to do so.

My Democratic colleague on the committee, Congresswoman Anna Eshoo of California, and I have introduced the Pancreatic Cancer Research and Education Act that would do just that. It has broad bipartisan support with 245 cosponsors. We believe this bill is the important first step toward improving the changes of survival for pancreatic cancer patients.

Thank you very much, and I yield back the balance of my time.

Mr. PITTS. The Chair thanks the gentleman and now recognizes the ranking member of the full committee, Mr. Waxman, for 5 minutes for opening statement.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you very much, Mr. Chairman.

Today we have the great pleasure of hearing from the Director of the National Institutes of Health, Dr. Francis Collins. In addition to his responsibilities as the head of NIH, Dr. Collins is a renowned researcher who, among many other scientific achievements, led the government's effort to map the human genome. We are delighted to have you with us, Dr. Collins.

Regardless of our political point of view, Democrats or Republicans, I know all members agree that NIH is one of the Federal Government's real gems. Indeed, across the country and around the globe, NIH is viewed as the preeminent biomedical research institution. And with good reason. NIH research has resulted in not only cutting-edge scientific breakthroughs, it has also led to real and meaningful improvements in the public's health.

From its work on cancer to hepatitis B; hypertension to the H1N1 virus; HIV/AIDS to Alzheimer's disease, to name just a few of our most pressing medical concerns, NIH researchers have made discoveries, developed treatments, and even found cures allowing us to live longer, healthier, and more productive lives.

But the work of NIH is never done. As we learn more about disease and the human condition, the list of research challenges grows. Some 40 years ago, for example, we thought a single, targeted war on cancer was all that we needed to wipe out that illness. Today, of course, through the efforts of NIH, the National Cancer Institute, we understand that cancer, in all of its many forms, is a far more complex situation. It is, in fact, a series of diseases with some unexpected commonalities in tumors from one disease site to the next. Thus, the NIH portfolio of cancer research has grown significantly and become more sophisticated and multifaceted.

Because of its outstanding work, we continue to look to NIH to help solve the trickiest of medical riddles such as diabetes, autism, MS, spinal cord injury, and Parkinson's disease, among others. And we must also look to NIH to figure out how to prevent disease and disability wherever we can.

Meeting these expectations demands nothing less than the best researchers, exceptional grant applications, strong leadership, and

sustained funding. Our job, the job of Congress, is to ensure that NIH has the stable funding it needs to continue its world-class work and global leadership. Money is in short supply, I know, but Federal support for NIH is not where we can afford to cut back.

At this juncture of endless research possibilities, both basic and translational, and tough economic times, Dr. Collins comes before us to discuss how he and NIH expect to address these major challenges. We are looking forward to his testimony.

I worry about the sequestration and automatic cuts in programs that will happen. I am glad I voted against that bill that calls for mindless sequestrations on the budget, domestic spending as well as defense spending. It is not the way to run a government, and of course, you are faced with that cloud hanging over your head. It is unfair and it is unfortunate.

I have additional time, and I would like to yield it to Ms. Schakowsky.

OPENING STATEMENT OF HON. JANICE D. SCHAKOWSKY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Ms. SCHAKOWSKY. Thank you for yielding.

Dr. Collins, I am so happy to see you here before this committee, and I am such a great admirer of yours. My good friend, Dr. Paul Farmer, who is known for his international work, spoke at a graduation ceremony at Northwestern and he was saying that sometimes bureaucracies are hampered by a failure of imagination, and when I think of someone who is not so limited, I think of you, Dr. Collins, as someone who really is a visionary in the possibilities of how the United States can be such a great leader in developing the cures and the treatments for diseases that have plagued us for so long.

I also want to thank you for your role in the implementation of a part of the Affordable Care Act, Obamacare, the patient-centered outcomes research provisions. There are a number of things in Obamacare I think that will make your job easier. The ACA authorized Cures Acceleration Network program and elevates the National Center on Minority Health and Health Disparities at NIH.

I look forward to your testimony and doing everything I can to help you in your mission. Thank you.

Mr. PITTS. That completes the opening statements of the members.

We have one witness today, and I would like to introduce today's witness at this point. Dr. Francis Collins is the Director of the National Institutes of Health. As Director, he oversees the work of the largest supporter of biomedical research in the world, spanning the spectrum from basic to clinical research. Dr. Collins is an elected member of the Institute of Medicine and the National Academy of Sciences. He was awarded the Presidential Medal of Freedom in 2007. He has received the National Medal of Science in 2009. We are very happy to have you with us today, Dr. Collins. Your written testimony will be made a matter of record. You are recognized for 5 minutes to summarize your testimony before the Q&A.

**STATEMENT OF FRANCIS S. COLLINS, DIRECTOR, NATIONAL
INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND
HUMAN SERVICES**

Mr. COLLINS. Thank you very much, and good morning, Mr. Chairman and members of the subcommittee. I want to thank each of you for your continued support of NIH's mission, which is science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability, and some of my material will be up here on the slides.

I couldn't help but also notice in this morning's Washington Post an op-ed from Fareed Zakaria pointing out also the economic benefits of which this particular author was taken by, for instance, that \$3.8 billion that the Human Genome Project required from the government sources led to \$796 billion in economic activity and raised \$244 billion in personal income within the first 7 years of its completion. So certainly we also would say that medical research is not just good for your health, it is good for the economy as well.

In my written testimony, I have summarized some of the numerous challenges and opportunities that NIH faces, and understanding you want me to be brief in my opening statement, I am just going to focus on a few points.

One is that you asked me to update you on implementation of the NIH Reform Act of 2006 and to report on this new National Center for Advancing Translational Sciences, or NCATS, as we call it. About 7 years ago, this committee began work on an ambitious reauthorization of NIH. Your goals were clear: give NIH's scientific leadership greater flexibility to pursue new research opportunities, create new mechanisms and structures to enable swift and facile collaboration amongst NIH's 27 institutes and centers, and increase the transparency in NIH's portfolio and the accountability of its scientific management. The technological revolution we are seeing right now in biomedical research and the flexibilities that you granted NIH in the Reform Act have enabled us to respond more nimbly to a major challenge in getting therapies to patients.

In recent years, as you can see here, researchers have succeeded in identifying the causes of more than 4,500 diseases. That is the good news. But unfortunately, treatments only exist for about 250 of them.

So at the same time we have all these new molecular targets within our sights, we face a situation in which only a few of the thousands of compounds that enter the drug development pipeline will make it into the medicine cabinet. As you can see here, it takes an average of 14 years for an idea of a new therapeutic to actually reach the market, and the failure rate is more than 95 percent, and when you have to add up the costs of all those failures, it takes a billion dollars or more to bring a drug to market.

An engineer looking at this pipeline would say wait a minute, there has got to be a better way. To address this challenge, I asked the Reform Act Scientific Management Review Board to consider whether there is more that NIH could do in collaboration with the private sector. They studied the issue intensively, took much public testimony, and in December 2010 they endorsed the creation of a new center, a National Center for Advancing Translational

Sciences specifically to address the bottlenecks in the discovery pipeline. So now working in collaboration, not competition with the private sector, NCATS is designed to support rigorous scientific research to reengineer the drug development process and move basic research findings into treatments for patients more quickly and more safely. The path to the creation of NCATS followed the guidelines you put forward in the NIH Reform Act, and NCATS was created on December 23rd of last year.

Just 4 months later, NIH was able to announce a major new initiative entitled “Discovering New Therapeutic Uses for Existing Molecules,” so how does this work? Working with several pharmaceutical companies, NCATS is offering scientists a shortcut: access to drugs that have already been tested and proven safe in humans but failed to show efficacy for the original application. Investigators in academia or in small businesses will have the chance to see if these drugs might work on other conditions or diseases.

As an example of how this could work, consider that AZT was developed as a cancer drug but it became the first effective therapy for AIDS patients. Another example, raloxifene, developed for osteoporosis, now found to be highly effective for breast cancer. We want to make this approach of repurposing more systematic.

So in a nutshell, here is how this will work. Eight companies have agreed—you can see them here—to make a total of 58 compounds available through NIH—we are the matchmaker—to researchers all across the Nation. Each of these compounds has already had tens or sometimes hundreds of millions of dollars of private money invested in its development and it is now being crowdsourced to researchers in all sectors to find new uses for these old drugs. The goal is to find new ways of helping patients who suffer from diseases that currently lack a treatment.

Let me just conclude by saying something about a patient’s story that illustrates the promise we see every day in NIH research as we seek to address the challenges of Alzheimer’s disease, cancer, Lyme disease, influenza, obesity, diabetes, and many other research frontiers. I want to tell you about Kathy Hutchinson. She is a 58-year-old woman who became a quadriplegic after suffering a devastating brain-stem stroke 15 years ago. Now, just last month, NIH-supported researchers reported using a neuro interface called Brain Gate to train Ms. Hutchinson to use her own thoughts to control the movements of a robotic arm. Those results were published in the journal *Nature*, and this video shows Kathy using the robotic arm in an attempt, using just her thoughts, to pick up and take a sip of her coffee. On that very first day she was successful. I think the smile on Kathy’s face and on the face of the young researcher behind her tells you everything you need to know about the promise of NIH research in just this one example.

So thanks for your time and interest this morning and thank you for your support of NIH. I look forward to your questions.

[The prepared statement of Mr. Collins follows:]



**Testimony Before the Health Subcommittee
of the Energy and Commerce Committee
United States House of Representatives**

Statement of Francis S. Collins, M.D., Ph.D.,
Director, National Institutes of Health

U.S. Department of Health and Human Services

6/21/2012

I. Introduction

Good Morning Chairman Pitts and Members of the Subcommittee. I am Francis S. Collins, Director of the National Institutes of Health (NIH), an agency of the U.S. Department of Health and Human Services (HHS).

Due to the steadfast support of this Administration, the Subcommittee, Congress, and the American people, NIH continues to be the most prestigious biomedical research agency in the world. I thank each of you for your continued support of NIH's mission to seek fundamental knowledge about the nature of living systems and to apply it in ways that enhance human health, lengthen life, and reduce suffering from illness and disability.

I have been asked to update you on the implementation of the NIH Reform Act of 2006 (Public Law 109-482), review how NIH sets scientific priorities at a time of unprecedented scientific opportunity, and report on the new National Center for Advancing Translational Sciences (NCATS). I welcome this opportunity to appear before you and brief you on some of what NIH has accomplished and what we hope to achieve to address the devastating burdens of disease and disability.

NIH Facts and Figures:

NIH is the largest funder of biomedical research in the world and our FY 2012 budget is \$30.86 billion. NIH's extramural research program represents 83 percent of our budget and supports about 50,000 research projects and research training awards and more than 300,000 scientists and research personnel at more than 2,600 universities, medical schools, and other research institutions in the United States. Every

state, along with nearly every Congressional district, receives NIH research funding. Approximately 11 percent of our budget funds nearly 7,000 intramural scientists working at the NIH campus in Bethesda, in laboratories in Baltimore, Rockville and Frederick, Maryland; at Research Triangle Park near Raleigh, North Carolina; at the Phoenix Epidemiology and Clinical Research Branch in Phoenix, Arizona; and at the Rocky Mountain Laboratories in Hamilton, Montana.

Public Health Benefits:

NIH basic research and translational and clinical advances have sparked a revolution in the diagnosis, treatment, and prevention of disease. Biomedical research funded by NIH has prevented immeasurable human suffering and yielded economic benefits as well as helping tens of thousands of U.S. citizens live longer, healthier, and more productive lives. These benefits include:

- a nearly 70 percent reduction in the death rate for coronary disease and stroke in the last half century;
- a nearly 30 percent decline over the last three decades in the age-standardized prevalence of chronic disability among American seniors;
- a 40 percent decline in infant mortality over 20 years; and
- more than 150 FDA-approved drugs and vaccines, or new uses of existing drugs.¹

Just a month ago, the Centers for Disease Control and Prevention (CDC) reported that among U.S. adults who suffer from diabetes, cardiovascular disease-related death declined by 40 percent and mortality from all causes declined by 23 percent between 1997 and 2006.² This drop in deaths due to diabetes is encouraging and is in large

¹ Stevens, A.J., et al., "The Role of Public-Sector Research in the Discovery of Drugs and Vaccines." *N. Engl. J. Med.*, 364: 535-41, 2011.

² Gregg EW, Garfield S, Cheng YJ, Geiss L, Saydah S, Barker, L, Cowie C. Trends in Death Rates Among U.S. Adults With and Without Diabetes Between 1997-2006. *Diabetes Care* 2012; 35: 1252-1257.

measure due to NIH-funded research that has enabled us to better understand and manage this disease.³ But it also underscores the urgency of NIH's research mission: we must fight the obesity epidemic in our population and prevent type 2 diabetes in the first place. We will not prevail against these twinned epidemics of obesity and diabetes without research supported and performed by NIH.

II. Implementation of NIH Reform Act of 2006

About six years ago, this Committee began work on an ambitious reauthorization of the NIH. The Committee's goals were clear: give NIH's scientific leadership greater flexibility to pursue emerging research opportunities, create new mechanisms and structures to enable swift and frictionless collaboration among NIH's 27 institutes and centers, and increase the transparency in NIH's portfolio and the accountability of its scientific management.

Today I can report that we are using new structures and mechanisms to enable and expedite trans-NIH research managed by the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) and funded by the Common Fund. We have increased transparency with online research inventories and portfolio databases. And we have worked closely with the Scientific Management Review Board (SMRB), instituted by the Reform Act, which has proven an effective advisor for providing expert advice about NIH's organization, management, and performance.

³ UnitedHealth Center for Health Reform & Modernization (2010). The United States of Diabetes: Challenges and opportunities in the decade ahead. Working Paper 5, November 2010. (http://www.unitedhealthgroup.com/hrm/unh_workingpaper5.pdf)

DPCPSI and the Common Fund:

The NIH Reform Act established DPCPSI to identify research that addresses important areas of emerging scientific opportunity, emerging public health challenges, and knowledge gaps. Research addressed by DPCPSI must merit special emphasis, benefit from additional research involving collaboration between two or more institutes or centers, or otherwise benefit from strategic coordination and planning. The Act also authorized the Common Fund, which includes programs from the former NIH Roadmap for Medical Research, to support this innovative research. The Common Fund was developed to change the way research is conducted – the way investigators approach their work, the tools they use, and the data and resources that are available to them. As the first Roadmap programs are reaching their tenth and final year, payoffs are beginning to be realized and the academic research culture has changed as investigators now routinely embrace interdisciplinary, multi-investigator-led projects. The Common Fund programs are transformative, synergistic, catalytic, crosscutting and unique.

Each year, NIH initiates a strategic planning process to identify the most pressing research needs and the most compelling scientific opportunities to support via the Common Fund. Gathering input from NIH stakeholders is a critical part of this process, as is an assessment of the current research portfolio. Through the Common Fund, NIH has funded the development of tools, technologies, data sets, and fundamental science that are relevant to health research broadly. The Common Fund now supports over 20 programs. Most of these programs consist of a series of integrated initiatives that collectively address a set of goals that aim to transform the way research is conducted,

the way that health and disease are understood, and the way that diseases are diagnosed or treated. Some examples include:

- The Human Microbiome Project (HMP) is systematically exploring the complex array of microorganisms that live on and in the human body, and play a critical role in health and disease. The HMP has developed a reference collection of 178 microbial genomes, including 30,000 newly discovered proteins as a resource for the scientific community. Demonstration projects have identified correlations between disturbances in the microbiome and diverse illnesses such as neonatal intestinal disease, cystic fibrosis, obstructive lung disease, and chronic sinusitis.
- The Patient-Reported Outcomes Measurement Information System (PROMIS) program has developed tools for the quantitative measurement of patient-reported outcomes for an array of diseases and conditions, including pain, depression, and fatigue. The PROMIS tool quickly is becoming the standard for measuring patient-reported outcomes during clinical studies.
- The Structural Biology program is pioneering new technologies to enable structural determination of proteins embedded in cell surfaces. These proteins represent the vast majority of targets for drugs but have been difficult to analyze. This Common Fund program is developing methods for the purification and analysis of these proteins which are helping in the design of new drugs. For example, a collaboration between researchers from the Structural Biology program and the Molecular Libraries program led to the discovery of a new drug that has completed phase 1 safety trials and is now in phase 2 trials for multiple sclerosis and inflammatory bowel disease.
- The Interdisciplinary Research program tested new mechanisms of fostering novel approaches to complex problems through interdisciplinary science. For example, the NeuroTherapeutics Research Institute involved scientists from disciplines such as neurology, neurophysiology, developmental pediatrics, psychiatry, chemistry, and mouse behavior to investigate the neurodegenerative disease Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), which causes tremors, imbalance, and dementia. These researchers discovered that in a mouse model of FXTAS, damage to neurons is evident early in life, highlighting the need to develop early biological, chemical, and behavioral interventions despite the appearance of symptoms later in life.

The Common Fund's High Risk/High Reward (HRHR) Program is another exciting initiative, which dedicates funding to foster innovation and creativity. HRHR enables the Common Fund to function like a "venture capital space" and support research that may

be considered unconventional and high-risk, but if successful, might transform our understanding of a wide range of biomedical problems, develop transformative tools and methods, or establish new clinical paradigms. The HRHR program emphasizes early stage investigators, who often have the most innovative ideas, but don't have the research "track record" to qualify for funding from more traditional grant mechanisms.

The Pioneer Award is designed to support a small number of investigators of exceptional creativity who propose bold and highly innovative new research approaches that have the potential to produce a major impact on broad, important problems in biomedical and behavioral research. The New Innovator Award program supports extraordinarily creative investigators within ten years of their M.D. or Ph.D. degree who have high impact research ideas but lack the preliminary data required for a traditional research project grant. The Early Independence Award allows exceptional scientists to "skip the post-doc" and move into independent research positions immediately after the completion of their graduate degrees. Outstanding scientists supported by these programs who have made notable contributions to research in a variety of scientific fields include:

- Karl Deisseroth, Pioneer Awardee: developed a set of tools to control subpopulations of neurons in the brain using light, in order to elucidate the precise brain circuitry that is affected in brain injury, Parkinson's disease, and many psychiatric diseases.
- Nathan Wolfe, Pioneer Awardee: established a surveillance system to monitor the entry of novel viruses into the human species, which may pose a significant threat to global public health.
- Adah Almutairi, New Innovator Awardee: developed a new "smart" polymeric material that could have widespread applications in drug delivery, surgical procedures, and medical implants.
- Aydogan Ozcan, New Innovator Awardee: created a portable, inexpensive, lensless microscope that can fit on mobile cell phones and be used to test for

pathogens in blood and water samples in remote regions where medical facilities are scarce.

Fostering innovation is a theme throughout the Common Fund. While this is an explicit goal of the High Risk/High Reward set of initiatives, it is an overarching goal of all of the programs. This investment in innovation is paying off economically, as well as scientifically, with patent applications, commercialization of technologies, and growth of new sectors in biomedical research. An Outcome Evaluation of the Pioneer Award Program revealed that three of the 22 awardees from the first two years of the initiative have applied for patents arising from their Pioneer research, and a fourth has licensed his technology for commercialization. Another Common Fund program, the Bridging Interventional Development Gaps program (formerly the Rapid Access to Interventional Development program) has led to 11 Investigational New Drugs, five of which have been licensed to companies for further development. The Molecular Libraries program has also led to many patent applications, and one molecule discovered through this program is now being tested in a clinical trial. This program has also contributed to a culture change in academic research by enabling all investigators to have access to chemical screening facilities equivalent to those of the pharmaceutical industry. Molecular screening centers have proliferated beyond the Common Fund set of centers, such that a 2010 evaluation indicated that 48 centers exist outside the Common Fund programs. This exemplifies how Common Fund programs can have significant impact beyond the immediate boundaries of their awards.

Transparency:

As directed by the Reform Act, NIH successfully implemented electronic systems to code uniformly the research grants and activities of all NIH institutes and centers. The Research, Condition, and Disease Categorization (RCDC) system provides consistent and readily-accessible information to the public about NIH-funded research, providing a complete list of all NIH-funded projects, beginning with fiscal year 2008, in each of 233 reported categories of disease, condition, or research area. We also created the Research Portfolio Online Reporting Tool (RePORT) which provides public access to reports, data, and analyses of NIH research activities, including information on NIH expenditures and the results of NIH supported research. By developing these tools, we provide better, more consistent and more accessible information about our research.

Management Review:

Finally, the SMRB established by the Reform Act issues reports detailing recommendations to the appropriate agency officials, both at NIH and HHS, on whether and to what extent their organizational authorities should be used. The reports are then submitted to the Congress by the NIH Director. Since its first meeting in April of 2009, the Board has held 11 meetings and produced four reports; one of which made recommendations about how the NIH can best contribute to advancing the translational sciences. Most recently, the Board agreed to undertake an analysis of the NIH Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs—namely, to recommend strategies for how NIH can optimize its use of these funding mechanisms. Deliberations on this topic are just underway and will continue throughout next year.

III. Priority Setting:

With the responsibility to set scientific priorities comes an obligation to explain how we do this and demonstrate that we are being good stewards of taxpayer dollars. Let me discuss the four principles that govern how we set our research priorities.

First and foremost, NIH responds to public health needs. These needs, whether an emerging infectious disease or the growing burden of chronic disease management on patients, our health care system and our economy, are addressed through a complex balance among basic, translational, and clinical sciences. The incidence, severity, cost, and sheer human suffering associated with specific conditions are also factors in how we set research priorities.

Secondly, NIH applies stringent critical peer review, provided by outside scientists who are experts in a given field, to rank the scientific opportunity and quality represented by the research proposals submitted. This intense competition has always assured that NIH research is of the highest scientific quality.

Thirdly, scientific history has repeatedly demonstrated that significant research advances occur when new findings, often completely unexpected, open up new experimental possibilities and pathways. We constantly are assessing our research portfolio in light of what the latest science suggests. Frustratingly, not all disease or scientific problems are equally ripe for new advances, nor do such advances come at the same rate across the portfolio, no matter how pressing they might be for the public's health.

Finally, we strive to ensure the diversity of NIH's research portfolio. We simply cannot predict the next scientific revelation or anticipate the next opportunity. If you think of scientific priority-setting as a series of thousands of doors that we might open—when we cannot know what is behind any one door—you can appreciate the challenge of setting priorities and the need for a broad research portfolio.

IV. Technology is Driving Science: NCATS as NIH Response

The new structures, mechanisms, and flexibility given to NIH by the Reform Act came at an especially opportune moment in scientific history. The technological revolution that we are seeing in biomedical research and the flexibilities have enabled us to respond more nimbly to what I consider the major challenge in getting therapies to patients. Let me talk about technology first.

In his biography, Apple founder Steve Jobs is quoted as saying that a “silver lining” in his battle with pancreatic cancer was that his son Reed had been able to “spend a lot of time studying with some very good doctors.” Jobs goes on to say that his son’s enthusiasm for biomedical research:

... is exactly how I felt about computers when I was his age. I think the biggest innovations of the twenty-first century will be the intersection of biology and technology. A new era is beginning, just like the digital one was when I was his age.⁴

Jobs was correct: today technological advances are driving science. We need look no further than the cost of DNA sequencing to see this dynamic at work. The cost

⁴ Isaakson, Walter, Steve Jobs (New York: Simon & Schuster, 2011) 539.

curve for sequencing is dropping at a breathtaking rate; sequencing speed has increased even faster than computer processing speed. What's more, the average cost of sequencing an entire genome has fallen from about \$3 billion 12 years ago, to \$10 million five years ago, to about \$7,700 today. Two U.S. companies recently announced that they are manufacturing machines that will sequence an individual's genome for approximately \$1,000, and that the first such instruments will go on sale before year's end. Lower sequencing costs likely will revolutionize how clinicians diagnose and treat diseases and enable the research community to pursue previously unimaginable scientific questions.

The Problem:

Even as we face the amazing and nearly innumerable scientific opportunities provided by this technological revolution, the development, testing, and delivery of new diagnostics and therapeutics remains a complex, costly, and risk-laden endeavor. In recent years, researchers have succeeded in identifying the causes of nearly 4,500 diseases, but we have been unable to turn this knowledge into many new therapies: effective treatments exist for only about 250 of these diseases. At the same time that we have all these therapeutic targets within our sights, only a few of the thousands of compounds that enter the drug development pipeline ultimately will make it into the medicine cabinet. It takes an average of 13 years at a cost of more than \$1 billion to

bring a drug from target discovery to market. And along the way, more than 95 percent of potential therapeutics fail.⁵⁶⁷

To address this challenge, I proposed and the SMRB endorsed the creation of NCATS to address these frustrating bottlenecks in the therapeutic discovery pipeline. Working in collaboration, not competition, with the private sector, NCATS is designed to support rigorous scientific research aimed at reengineering elements of the drug development process and moving basic research findings into new treatments for patients more quickly and safely.

Teaching Old Drugs New Tricks:

On May 3rd, HHS Secretary Kathleen Sebelius and I announced the Discovering New Therapeutic Uses for Existing Molecules collaborative pilot program, in which compounds have undergone significant research and development by industry, including safety testing in humans, providing a head start or shortcut for scientists who want to test them for different therapeutic uses. This program aims to tackle an urgent need that is beyond the scope of any one agency, company, or non-profit. NCATS will manage the Therapeutic Discoveries program and match researchers with a selection of molecular compounds offered by companies to test their applicability for new therapeutic uses, with the ultimate goal of identifying promising new treatments for

⁵ DiMasi, J.A, Hansen, R.W., Grabowski, H.G., "The price of innovation: new estimates of drug development costs." *Journal of Health Economics* 22 (2003) 151-185

⁶ Collins, F.S., "Mining for therapeutic gold." *Nature Reviews*, Volume 10, page 397 (June 2011).

⁷ Paul, S.M., Mytelka, D.S., Dunwiddle, C.T, Persinger, C.C, Munos, B.H., Lindbort, S.R., Schacht, A.L. "How to improve R&D productivity: the pharmaceutical industry's grant challenge." *Nature*, Volume 9, pages 203-214. (March 2010).

patients. As an example of what we're trying to do with this new initiative, consider that AZT once was a cancer drug but became an important therapy for AIDS patients, and Raloxifene was originally developed for osteoporosis but has become highly effective in treating breast cancer.

NCATS has partnered with Pfizer Inc., AstraZeneca, Eli Lilly and Company, Abbott, Bristol-Myers Squibb Company, GlaxoSmithKline, Janssen Pharmaceutical Research and Development L.L.C., and Sanofi. These eight companies have collectively agreed to make nearly 60 compounds available for the pilot program.

This is just one example of how NCATS will conduct and support research to develop enhanced methodologies and approaches in translational science that can be used by other NIH institutes and centers, academia, industry, and other sectors. Moreover, as NCATS advances our understanding of scientific targets and pathways, new avenues for scientific inquiry will be stimulated and pursued, ultimately reaffirming NIH's commitment to investing in basic science research.

V. U.S. Biomedical Research Leadership

NIH funding is the foundation for long-term U.S. global competitiveness in industries such as biotechnology, drug development, medical devices, and health care. So great is the return on our national investment in research, United for Medical Research and the Information Technology and Innovation Found reported that in 2011, a \$1 billion investment in medical science is projected by economists to increase gross

domestic product by roughly \$6 billion.⁸ This same report stated that U.S. life sciences companies support more than 7 million jobs and account for \$69 billion in U.S. economic activity.⁹

VI. Promise of NIH Research: Grand Challenges

Let me conclude my testimony by offering a few examples of where we see the greatest hope—and the greatest urgency—for more scientific investigation that leads to new understanding and new therapies.

Alzheimer's Disease:

As many as 5.1 million Americans currently suffer from Alzheimer's disease; more than 280,000 Americans will be diagnosed with the disease this year, with nearly 800 of our fellow citizens being diagnosed every day. By the year 2030, the last baby boomer will turn 65 and 7.7 million Americans over the age of 65 will have Alzheimer's disease.¹⁰ Today, Alzheimer's and other dementias cost the U.S. economy more than \$180 billion a year and if no cures and therapies are found, will cost the United States \$1.1 trillion annually by 2050. Fortunately, new scientific advances have been showing remarkable promise, especially in the last few months.

Using mice genetically engineered to make the abnormal human *tau* protein—a protein already identified in the brains of Alzheimer's patients—scientists found that Alzheimer's disease appears to spread through the brain in much the same way that an infection moves through the body. The abnormal *tau* protein started in one area of the

⁸ Atkinson, Robert, *et al.*, "Leadership in Decline: Assessing U.S. International Competitiveness in Biomedical Research." *Information Technology and Innovation Foundation and United for Medical Research* 5 (May 2010).

⁹ *Id.* at 2.

¹⁰ Alzheimer's Association, 2011 Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia, Volume 7, Issue 2

brain in the mice and, over time, spread from cell to cell to other areas of the brain in a pattern very similar to the earliest stages of human Alzheimer's disease. The discovery of the *tau* pathway could influence the direction of future research and give investigators a target for drug development that might arrest Alzheimer's disease progression at very early stages when the disease is most amenable to treatment.¹¹

Alzheimer's disease also stands to benefit from translational research by way of drug rescuing and repurposing. Recently, a team that included NIH-supported investigators reported that bexarotene, a drug compound originally developed for treating T-cell lymphoma (a dangerous type of white blood cell cancer), was capable of clearing the protein beta-amyloid quickly and efficiently after only a short exposure to the compound in Alzheimer's disease mouse models. Beta-amyloid accumulates in the brain of Alzheimer's patients due to an impaired ability to clear the protein, leading to a build-up of beta-amyloid plaques and ultimately neuronal death. These findings are exciting because, in time, they could benefit patients with Alzheimer's disease. Researchers are especially hopeful because the drug used in the research has been studied already in humans, providing a wealth of information about dosage and toxicity.¹²

We are working to design additional non-invasive ways to detect the early brain changes characteristic of Alzheimer's disease. In the near term, we hope to develop drugs or other therapeutic strategies to delay the onset of Alzheimer's disease by a

¹¹ Liu L, Drouet V, Wu JW, Witter MP, Small SA, et al. (2012) Trans-Synaptic Spread of Tau Pathology In Vivo. PLoS ONE 7(2): e31302. doi:10.1371/journal.pone.0031302

¹² Cramer PE, Cirrito JR, Wesson DW, Lee CYD, Karlo JC, et al. (2012) ApoE-Directed Therapeutics Rapidly Clear β -Amyloid and Reverse Deficits in AD Mouse Models. <http://www.sciencemag.org/content/early/2012/02/08/science.1217697.full.pdf>

decade or more. And we are building new public-private partnerships to speed drug development by repositioning abandoned compounds.

Precision Medicine for Cancer:

Mutations in the genome of individual cells are what cause cancer, most often in response to something encountered in the environment, and cause good cells to go bad. Advances in DNA sequencing are now making it possible to identify the precise mutations that cause a normal cell to become malignant. The Cancer Genome Atlas is moving swiftly to sequence the tumor genomes of hundreds of cases of each of the twenty most prevalent forms of cancer. Such new knowledge is enabling us to discover new pathways and develop entirely new forms of targeted therapy. Soon, we may be able to apply this technology to allow every tumor in every cancer clinical trial to be sequenced within a few days of biopsy, allowing for a choice of the optimal therapy for each patient. Another opportunity we are pursuing is the development of new cancer biomarkers, including DNA circulating in the bloodstream, to identify responses to a given therapy. We hope to then use our knowledge of these responses to apply combination-targeted therapies and aim not only for response, but for cure.

Reverse the National Epidemic of Obesity:

The rising prevalence of obesity in the United States, especially in children, threatens to erase the gains in longevity achieved over the past decades. And, as I mentioned earlier, an increase in obesity brings an increase in its twin epidemic, diabetes.

To stem this epidemic, we are working to develop an evidence-based approach to helping people change their diets and personal habits. We also are exploring how to precisely define the molecular pathways that control weight. We hope to learn more about how diet and genetics interact at the level of the individual to increase the risk of diabetes and cardiovascular disease.

Secure an AIDS-free Generation:

In the past few years, NIH-supported researchers have learned that if people who are HIV-infected are diagnosed quickly and given HIV medications before they develop AIDS, the likelihood that they will transmit the virus to others is reduced by 96 percent.¹³ This means that in the near future, a United States high school graduate might become part of the first AIDS-free generation in the country since the epidemic began. We also have the chance to build on recent advances to develop an effective vaccine against the human immunodeficiency virus itself, a goal that has frustrated us for thirty years.

Conclusion

Mr. Chairman and members of the Subcommittee, I offer these examples of the hope and promise that NIH research holds in part to thank you for your past support of NIH, but also to urge that you continue to invest in lifesaving biomedical research. NIH contributes to our economic growth and has secured our nation's leadership of the life sciences in the 21st century, but what motivates the scientific community has always

¹³ Cohen, Myron S. et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. 2011. New England Journal of Medicine. 365: 493-505. doi:10.1056/NEJMoa1105243

remained the same: to apply the best science and medicine to end preventable human suffering from disease and disability.

Mr. PITTS. Thank you, Dr. Collins, for that wonderful testimony, and I will begin the questioning and recognize myself for 5 minutes for that purpose.

The grant process at NIH is very important, and hopefully is rigorous and transparent to ensure that the best projects that address the highest priorities are chosen. One step that generally raises a lot of discussion is the peer review process. I have a few questions about that process, if you can address them. First, how does NIH select reviewers and how are review panels formed? Secondly, what criteria do reviewers use and how are the criteria scored and how does NIH ensure that the criteria are applied? Take those two first.

Mr. COLLINS. Well, I very much appreciate your question, Mr. Chairman. Peer review is the main stay of how we make sure that the taxpayers' dollars are utilized to support the very best science. Our peer review system at NIH is considered as the gold standard for the rest of the world, but we are constantly trying to improve it. Basically, peer reviewers are chosen in a particular area of science and medicine because of their expertise. We seek to identify those who have both detailed expertise about a technology that may be under a review but also a broader picture about where that particular field has been and where it is going. The reviewer choices are made by our scientific staff, and these are scientific review administrators who are talented, doctoral-trained individuals who have chosen, many of them out of a feeling of public service, to give their careers to this effort of making sure our peer review process is done in a fashion that is as exquisitely correct as possible.

Those reviewers are then brought together. They are given a series of grants that have been received. They are assigned so that each grant has oftentimes a primary and a secondary reviewer who read it in great detail but the entire study section looks at all of the grants. And then there is a discussion about what the merits are and what the risks are in terms of failure of particular proposals. The reviewers then are asked to assign a numerical score to that particular application between one and nine. One is good; nine is not good. And they debate around the table the merits of this, so there is a real-time conversation so that everybody in the room has a chance to weigh in and you learn from those who maybe know something special about this. And they vote not only a single priority score and overall priority score but also for various characteristics, and one of the ones that we recently added is innovation. We want a specific priority set on the basis of innovation.

When the dust all settles, those scores are tallied up, averaged, then that is reported to our second level of review, which are the advisory councils that each of the 27 institutes has at their disposal and they aim to try to balance out the portfolio. The first level is about scientific merit. The second level is, where are the needs greatest here in terms of where medical research needs to fill in gaps.

Mr. PITTS. OK. A couple of other questions I had. Are there different levels in the review process and who makes the final decision? Can applicants appeal the review process? And how does NIH provide transparency for the research funded at NIH, Web sites,

databases? Who is responsible for overseeing the databases and ensuring that they are current?

Mr. COLLINS. So the final decision ultimately after these two levels of review is made by the institute director, who is presented with the final results and then signs off on them. In terms of transparency, the way in which all of the funded grants are made is available is through a Web site, which is very heavily utilized called Reporter. I would encourage you to go and have a look if you want to see what it is that we are funding and the roughly 50,000 grants that are currently being supported. You can see there from the abstracts what the research is all about, who the investigators are, what the goals are.

Mr. PITTS. All right. Maybe you could have your staff meet with our committee staff to go over the process a little bit more. We have some other questions that we could ask, if you would.

Mr. COLLINS. I would be very happy to.

Mr. PITTS. One final question. NIH has been working closely with the FDA on regulatory science and other matters. Are you working with the FDA to craft a timely clearance pathway for next-gen sequencing, and if so, what specific role are you playing?

Mr. COLLINS. So the FDA has for many years been looking at the very rapid advances in DNA sequencing, and now with the costs having come down from perhaps \$100 million to sequence a genome 10 years ago to less than \$10,000, there is a great deal of interest in having this find its way into medical care for many different conditions, particularly cancer. FDA has been studying carefully the issue about how to oversee that kind of DNA testing, given that much of it is done in laboratories as opposed to being distributed in kits, and that discussion is still going on in terms of how to balance the desire to be sure that individuals are given credible information that correctly can advise them about their medical care but not do so in a heavy-handed way that would slow down this remarkable innovation that is happening right now.

I brought along with me, by the way, a DNA sequencing machine. When I was in charge of sequencing the human genome, the sequencing machines were as big as phone booths. This is what they look now. The sort of marriage of biotechnology and integrated circuits has happened and it is pretty impressive.

Mr. PITTS. Thank you. My time has expired.

I yield 5 minutes to the ranking member, Mr. Pallone, for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

Dr. Collins, during these tough times, we in Congress are often told that without sustainable budgets and some degree of certainty, it is not feasible to maintain growth and development in the private sector. So I wanted to ask you with regard to the public sector, NIH, how does operating on continuing resolutions and the threat of a sequestration affect your ability to maintain constant funding to the best and brightest scientists and adequately address the numerous health burdens represented in the NIH research portfolio?

Mr. COLLINS. Well, thank you for the question. It does make it challenging when science really is best sustained by having stability so that investigators out there in all the States of our Nation and some outside our Nation are able to pursue research with the

confidence that there is going to be some support that will not just become somewhat questionable the next year or the next month, and certainly, given the fact that the NIH budget has to be decided upon every year and it rarely has been decided by October 1st, as you all know, it does make it challenging in terms of how we as science managers try to steer this ship, particularly now with the uncertainty about the sequesters, which have already been raised. That puts a very significant source of concern as we try to plan where science should go.

Most scientific projects do not have a cycle time of a few months. It is more like 3 or 4 years. And so if we are deciding to start down a path with a particular project, we expect to be able to assure that investigator that we are going to support it for that 3 or 4 years. Otherwise the initial money to go to waste. But yet when we don't know from year to year exactly what our resources will be, that makes it very tough.

I was at the BIO meeting yesterday in Boston. This is the Biotechnology Industry Organization. It's their international meeting. And I listened to the discussion at the lunch panel about how the instability in the private sector makes it really hard for biotech companies to know what to do, and boy, did I relate to that. I think we all have the same issue that stability would be a very desirable pathway if we could achieve it.

Mr. PALLONE. Thank you. I wanted to ask you about pancreatic cancer research. Part of the reason is personal because my mother passed not long after she was diagnosed with pancreatic cancer. Despite years of funding for cancer research, pancreatic cancer still has a terribly low survival rate with only about 6 percent patients diagnosed with pancreatic cancer alive 5 years later. So in my opinion, in talking to others, there doesn't seem to be any real improvement in survival for over 30 years. Yet it is my understanding that only 2 percent of the NCI budget is devoted to pancreatic cancer research.

I know it is not an easy question, but can you explain why the overall cancer 5-year survival rate is 67 percent and the survival rate for pancreatic cancer is still just 6 percent? And what is NIH research strategy to improve survival rate for pancreatic cancer patients?

Mr. COLLINS. I appreciate the question, and Mr. Lance already raised this issue, and I am certainly personally very deeply concerned about the situation with pancreatic cancer, having just lost a friend, who is one of the founders of my field of medical genetics, a couple of weeks ago, Dr. David Rimoim. Clearly, with pancreatic cancer, one of the big problems is the inability to know it is there until it is already very far advanced. Recent data tell us that actually pancreatic cancer doesn't actually grow that quickly, but by the time somebody is diagnosed, they probably had the cancer for 15 or 20 years.

Mr. PALLONE. If I could interrupt you, I know in my mom's case it was because she was jaundiced because the tumor was affecting—

Mr. COLLINS. Pressing the bile ducts?

Mr. PALLONE. So it was manifested, and my understanding is, that is the only time usually or one of the few times you know, but in most cases they don't see the jaundice.

Mr. COLLINS. Exactly, because it is deep in the body in a place where one doesn't have the ability to know that there is a lump there. It doesn't create symptoms until very late. So one of the things we desperately need is new approaches to early detection, to catch those cancers a decade sooner where they probably then could be much better managed. There is a lot of interest and effort going on in terms of both imaging approaches and also biomarkers that might be circulating in peripheral blood that would give a hint that this disease was present long before it was otherwise apparent.

The other thing we need to do is understand how to treat this disease, and to understand that better, we need to know what is going on at the molecular level. We have major advances now happening for all cancers but a big focus on pancreatic cancer.

Mr. PALLONE. But it is a very little percent of your budget, though. Why is that?

Mr. COLLINS. Well, it is modest. I will say it has increased 311 percent in the last 10 years. So the increase in support for pancreatic cancer is greater than for other cancer types. Clearly, there is a great need to do something to move this along.

I will tell you, just recent at the ASCO meeting, there was a whole other set of data about a potential approach to this involving something called protein kinase C that looks extremely promising. The cancer researchers who came away from that said this was the most interesting, potentially exciting thing they had heard about pancreatic cancer treatment in a long time. So we are working on it.

I understand the frustration that people feel, and I am sure Dr. Varmus and I would be glad to continue that conversation. We have meeting with the pancreatic cancer folks and others. I hope we can work on this together.

Mr. PALLONE. Thank you.

Mr. PITTS. The Chair thanks the gentleman and now yields 5 minutes to the vice chairman, Dr. Burgess, for questions.

Mr. BURGESS. Thank you, Mr. Chairman, and Dr. Collins, again, thank you for spending time with us this morning.

Let me just stay on the issue of pancreatic cancer for a moment. I had some questions in that regard also. But in our conversation just days ago when you informed me about the chronicity aspect to pancreatic cancer, as a clinician, I am always aware that this is a difficult problem to treat. You can't palpate it. There are no skin changes, very little in the way of symptoms until it is well advanced.

So marry up, if you will, what might happen in the field of genomics as well as you referenced protein kinase C, which I assume is a new marker that may be available. Is there a way to couple the ability to discover a vulnerability through knowledge of the human genome with an aggressive marker campaign that actually might lead people who are in the chronic phase of pancreatic cancer, the pre-palpable form, if you will, that would then lend them

to a degree of earlier treatment than they have ever received before.

Mr. COLLINS. Doctor, that is a really wonderful model that we are very much embracing and trying to pursue. So how do we identify individuals at higher risk for this? We know about a few of those risk factors. Certainly, family history is one of them, and at least one gene, which happens to be a rather famous one for other reasons, the gene called BRCA2, which places women at risk of breast and ovarian cancer, also increases the risk of pancreatic cancer. So if we had an imaging modality that we were convinced was reliably able to detect a cancer which it is still small and surgically curable, we would want to apply it first to those individuals at higher risk and that is very much under consideration now.

But I think we also want to look for other kinds of markers beyond imaging that may help us detect the presence of disease at the earliest stage. Here is where the whole proliferation of science around the field of genomics is giving us windows into what is going on in the body that we didn't really have until very recently. Are there signals? Are there in fact evidences in the immune system that is reacting against the presence of a cancer that we could detect by looking at those immune cells, which of course circulate in the body. Those kinds of approaches are certainly very much on our front burner, but also the therapeutics. The protein kinase C delta looks as if—let me back up a second.

Almost every pancreatic cancer has a mutation in a famous gene called KRAS. It is a driver mutation. It is a major factor for why these good cells went bad. But we don't yet have a way of specifically targeting KRAS. That has not worked. It turns out that just downstream of that, there are other things that happen that are targetable, and that is where this PKC delta has come forward, giving some new ideas, and this is an important paradigm. As we learn more about how things are connected within the cell, even if you can't target the primary problem, you can sneak around and target something that is just upstream or downstream and achieve the same result. That is what a lot of science about cancer right now is aimed at.

There was a meeting going on organized by the AACR yesterday at Stanford. I am waiting to hear what other new ideas came from that in terms of pancreatic cancer diagnosis and treatment.

Mr. BURGESS. Now, is this an example of where that translational research that crosses all of the silos at NIH, is this where that is helpful?

Mr. COLLINS. Absolutely. Certainly, companies are intensely interested in developing cancer therapeutics. I have spent a lot of time with pharmaceutical companies in the last couple of years trying to be sure that we are partnering effectively, and cancer is an area where they are also very excited because of all these molecular studies. But there can still be those bottlenecks about how do you pick the right targets from a long list that is emerging from things like the Cancer Genome Atlas and then how do you, once you pick that target, move it quickly to the point where you can be confident it is going to be safe and potentially effective in a patient. There are all kinds of steps there.

Mr. BURGESS. And then are you equipped to deal with your counterparts at the FDA because there can be other bottlenecks outside of the walls of your hallowed institute that can present a problem?

Mr. COLLINS. Peg Hamburg and I when we first came to our respective roles at FDA and NIH formed a joint leadership council to tackle exactly this kind of circumstance. Are there areas where NIH and FDA can inform each other, work together, can we provide regulatory science platforms that would assist them in making decisions about what is safe and effective? Can they educate us about the ways in which investigators that we support could be smarter about how they design their approaches both pre-clinical and clinical so that they will end up with the data that FDA needs for approval.

Mr. BURGESS. In the brief time I have left, do you have a couple of examples that you could provide to us of things that have been successful?

Mr. COLLINS. So one that we are working on right now is a new approach to pre-clinical toxicology. Now, that sounds—when I was a medical school student, I would have thought must be a really boring science but it is actually really interesting. How do you decide that a particular chemical compound that you would like to try out in a clinical trial is safe to do that? Generally, we have used animal models—small animals, large animals—and we look for a signal that maybe that compound is causing trouble in liver or heart. Now we can do that more cleverly, and we are doing this as a partnership with FDA and with DARPA, the Defense Advanced Research Project Agency, building bio chips that are loaded up with human cells representing three-dimensional examples of human liver cells, heart cells, kidney, brain and so on, and using that as a test of whether a compound is safe or not by looking to see whether those cells get happy or unhappy when you give them a particular test substance. That could be much faster and much more accurate, and it is an example of how we and the FDA have gotten together and said there is a bottleneck, let us tackle it, let us do something about it.

Mr. BURGESS. Very good.

Thank you, Mr. Chairman. I will yield back.

Mr. PITTS. The Chair thanks the gentleman and now yields to the ranking member of the full committee, Mr. Waxman, for 5 minutes for questions.

Mr. WAXMAN. Thank you, Mr. Chairman.

Dr. Collins, it has got to be very difficult to go year by year without knowing what your budget is going to be. That has got to lead to a lot of instability. But you are facing something as other parts of our government much more dramatic at the end of this year, the sequestration. What it really means is across-the-board cuts that was called for in last year's budget agreement, and that will go into effect in January unless Congress changes things. It looks like are still deadlocked on changing things. By the Congressional Budget Office estimates, this would mean an approximately 8 percent reduction in NIH's budget, or roughly \$2.4 billion less available funding, taking NIH back to its 2004 funding levels.

If this funding went into effect, at least 2,300 fewer grants would be awarded. I assume this is on your mind and it is on the minds

of a lot of people back in my southern California district. People are talking about in the aerospace and defense industries, how do they make plans for the sequestration. And I know as a government leader, you have to make plans for your sequestration. What is your thinking about it? How would NIH absorb this \$2.4 billion in lost funding? What cuts would you make? Would you make it across the board? Would you pick and choose which institute and centers get hit, by how much? If you made a decision not just across the board, what criteria would you use to pick and choose?

Mr. COLLINS. Mr. Waxman, this is certainly on my mind. In fact, it is on my mind sometimes at 3 o'clock in the morning. If there is something that I am most concerned about in terms of an event that could really disrupt and do serious damage to the progress that we now see in medical research, this is it. You have correctly quoted the numbers as I understand them from the CBO about what the sequesters would do to NIH, and that loss of 2,300 grants, which would come already 3 months in the fiscal year, would represent about a quarter of the total grants we would give for that entire year.

Exactly how that would be distributed of course would depend upon scientific priorities but it would clearly stretch across all areas. There would be cuts in cancer and diabetes and heart disease. There would be cuts in common diseases and rare diseases. There would be cuts in basic science. There would be cuts in training. We would have to basically spread the pain. We wouldn't do it in a completely blind fashion like a haircut but everybody's hair would get cut pretty significantly. There would be a lot of people with very short hair at the end of this.

So I think maybe if people understood a little better than we have been able perhaps to convey just how much momentum there is right now and how much enthusiasm and anxiety there is amongst our biomedical research workforce, which is our most precious resources, the consequences of this perhaps would become more apparent. Clearly, if you are an investigator coming to NIH with your best and brightest idea, we already are at the lowest rates in history for success in getting your grant funded, about 17 percent, where we have traditionally been at 30 percent. To drop that even further, which would clearly happen dramatically were the sequesters to kick in, might deal a blow to many of those investigators that they simply would not be able to sustain.

Mr. WAXMAN. One of the reasons that we haven't been able to work all these problems out is that the Republicans, who run the Congress, are afraid to increase taxes even on billionaires. I have a lot of wealthy people that I know. A lot of them live in my district. I can't imagine if they heard these kinds of results would happen to NIH and other areas, they wouldn't be willing to say look, we will put in more money. This is an important function of the government. We shouldn't allow this to happen.

I was struck by the statistic in your testimony that we have identified the causes of nearly 4,500 diseases but only have effective treatments for roughly 20 percent of them so the new initiatives that we have in the Cures Acceleration Network sound very promising but we have got a lot of work to do, even if we get by the sequestration issue. Isn't that the case?

Mr. COLLINS. We do, and it is both a wonderful new opportunity because of this proliferation of new discoveries about the molecular causes of disease that we just didn't know until recently but we don't want to have them just sit there as publications that everybody says wow, look at what we have discovered. We want to move that forward to therapeutics.

I am working with the pharmaceutical industry on an initiative where together we might try to look at where are the highest-priority new targets because in many ways, there are so many of them now, you have to decide where is your best chance of success. So we just ran a pair of workshops on what is called target validation with industry R&D chiefs getting together with academic leaders and NIH to talk about how we could together move this forward in a way that will accelerate translation, accelerate moving that number that have diseases that can be treated higher and quicker. That is our goal.

Mr. WAXMAN. Thank you very much. My time is expired. I appreciate, Mr. Chairman, your calling on me.

Mr. PITTS. The Chair thanks the gentleman and now yields to the chair emeritus of the full committee, Mr. Barton, for 5 minutes for questions.

Mr. BARTON. Thank you, Mr. Chairman. I think we have got the answer to what to do about our deficit. We will just do a special tax on Chairman Waxman's rich people in his district. Apparently they want to pay higher taxes and Mr. Waxman wants them too, so if we can find a way to do it constitutionally, I will be a cosponsor of that bill.

Anyway, to get back to the hearing. Dr. Collins, you and I have had several meetings in my office, so I just want to get on the record some of the things that you have told me in our private conversations. What is your view of the Common Fund that the reauthorization bill back in 2006 created?

Mr. COLLINS. Well, Mr. Barton, Common Fund, I think, has been a brilliant addition to NIH's ability to support high-risk but high-reward projects that don't fit neatly within the remit of any one of the 27 institutes and centers but could actually have profound impact on all diseases and all organ systems. As the NIH Director, one of the most important opportunities I have is provided by the Common Fund, which you and Dr. Zerhouni discussed and which this committee then put forward and is now put in statute as part of what we are aiming to do in that space of sort of venture capital, and I think of it as our venture capital. And it has funded a variety of really quite remarkable projects. I will just mention one, the Human Microbiome Project, which was much written about in the last 10 days or so in the press because of a series of about three dozen publications that came out describing those microbes that live on us and in us in breathtaking detail in ways that clearly make it possible for us to understand how we interact with them for health or sometimes for disease. This is really a nice example of something that probably couldn't have happened without the Common Fund.

Mr. BARTON. What is the funding level right now in that fund? What is your balance?

Mr. COLLINS. It is about \$500 million, which means it is only about 1.6, 1.7 percent of the total NIH budget. The authorization would be carried all the way to 5 percent if the budget of NIH as a whole were able to grow. It has been difficult in the past few years to be able to change that.

Mr. BARTON. And how much do you obligate each year, approximately, from that Common Fund?

Mr. COLLINS. So most of the projects that are funded by the Common Fund are funded for 5 years so while it varies from year to year depending on what is moving out and what is moving in, then it would be roughly 20 percent of that 500, so about \$100 million.

Mr. BARTON. If Chairman Upton and Ranking Member Waxman, Mr. Pallone and Mr. Pitts were interested in doing another reauthorization bill at NIH, what are some items that you think should be included in that bill if we were to do a new reauthorization bill?

Mr. COLLINS. You know, I would have to think hard about exactly what would require that kind of step. You did such a good job in 2006 that many of the issues that needed attention were very effectively dealt with, so there is much a shorter list now, I think, of urgencies.

Mr. BARTON. If you could give that some thought and formally let the committee know, I would appreciate that.

Mr. COLLINS. I would be happy to.

Mr. BARTON. In my last minute and a half, I want to go to a little more sensitive subject, Title 42. As you know and the committee knows, this is a special title that gives the ability to pay above SES-level salaries to very special people to keep them in government service or to attract them to government service. It was intended to be sparingly used and for only exceptional or at least potentially exceptional employees. I think it has been misused. You may not share that view. Could you tell us what percent of the employees at NIH right now generally received Title 42 compensation?

Mr. COLLINS. So we have 19,000 employees at NIH and roughly 24.8 percent of them are in the Title 42 appointment mechanism. These are mostly individuals with doctoral-level training, and we have recently, working with HHS, instituted a new policy where only doctoral-level individuals will be eligible for Title 42 appointments, changing a practice that has been present in the past which we now feel we should not continue.

Mr. BARTON. And on balance, I know there is really no such thing as an average Title 42 salary, but could you give a general idea of what a Title 42 salary is as compared to the highest SES salary?

Mr. COLLINS. Well, the vast majority of Title 42 salaries are below \$200,000. Again, these are Ph.D. or M.D. or M.D./Ph.D level individuals. Only a small percentage, about 465, of these are at salaries above \$200,000, and those are the individuals at the highest level of seniority and expertise. Those are institute directors, people like Dr. Fauci. I have to tell you, Mr. Barton, and you and I have discussed this, if we did not have this hiring ability, we would not be able to recruit the best and brightest to come and join our scientific and medical workforce, and if one wants NIH to be the most excellent scientific and medical research organization in the world, we have to be able to recruit those people. We are still pay-

ing them less on the average that they could get in a university and much less than they could get in the private sector, and we are counting therefore on their public spiritedness, but at least to be in the game, Title 42 helps us to be able to maintain——

Mr. BARTON. I know my time is expired. I am preparing draft language to reform the Title 42 program. I will be sharing it with the committee leadership and NIH, and you had indicated that you had some thoughts too. If you would care to get those to my office, I would appreciate that.

Mr. COLLINS. I would be happy to do that.

Mr. BARTON. I thank the chairman for his discretion and yield back to the Chair.

Mr. PITTS. The Chair thanks the gentleman and would remind the members, we are going to be facing a time constraint when we hit the floor votes, so if you can constrain your time, please.

The Chair recognizes the gentlelady from Illinois, Ms. Schakowsky, for 5 minutes for questions.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman.

Dr. Collins, in a recent article you expressed concerns that if it gets worse than the current rate of one in seven grant applications receiving NIH funding, which would occur if NIH funding is cut, we may lose this generation of young researchers. Could you discuss what this would mean to our ability to discover new medical breakthroughs and to maintain our global leadership in biomedical research?

Mr. COLLINS. Well, certainly, young investigators and investigators in mid-career and our senior leaders are all feeling the stress here in terms of the difficulty of getting supported in the current climate whereas you mentioned and I cited earlier the success rates have fallen to the lowest levels that we have ever seen. That means that investigators spend an inordinate amount of their time writing new grant applications, just missing the pay line, revising, trying something else instead of actually doing the research, so it is a very inefficient use of their time.

Particularly for investigators just starting out, we are trying to identify a path for them. Are they going to be able to pursue the ideas that got them interested in this field in the first place? This can be very demoralizing when after several tries you still have not succeeded in receiving funds. We try to do everything we can to give those early-stage investigators a leg up. They compete against each other instead of against more experienced investigators, but there is only so much we can do. And clearly, I hear from them on a regular basis, those that have really kind of reached the end of the line and some of them are simply saying I can't keep doing this anymore, I am going to find some other kind of work; I will go to teaching instead of doing research, maybe I will go to law school, maybe I will think about another country. And certainly when it comes to those who have come to our scientific workforce from other countries and we have depended on that talent for many years and been greatly benefited by it and many of those individuals stay in our country and become our leaders, they are much less likely to do that with these stresses upon them and with much more attractiveness of positions being offered to them in places like China and India, which are increasing their support for biomedical

research at a dramatic rate even as ours is losing ground to inflation.

So it is not a pretty picture. If we are determined to maintain the leadership that America has enjoyed in biomedical research for the past 20 or 30 years, we can't just assume that that will happen because it has in the past. We clearly have to look, as a recent study done by the Information Technology Innovation Foundation, at how America is stacking up in global competitiveness, and it is not an easy thing to look at if one is interested in seeing our economic future be as bright as it needs to be.

Ms. SCHAKOWSKY. And what happens to the research itself aside from the researchers if there is a start and a stop? Are we hamstringing ourselves in that regard?

Mr. COLLINS. Certainly, science tends to build on itself, and if a good idea has been started and there is something that you have added to that that takes you in a new direction, you don't want to see that simply go on hold while waiting for the next cycle of potential research support, and certainly scientists are themselves people we invest in. You are talking about a doctoral-level individual at a university. We probably helped train them through a training grant or through their participation in research. So we already have a big investment in that person, and the idea that we might now lose that investment by not being able to sustain their career is a double loss.

Ms. SCHAKOWSKY. Thank you. In the interest of time, I will yield back, but I thank you, Dr. Collins, for your response.

Mr. PITTS. The Chair thanks the gentlelady and recognize the gentleman from Georgia, Dr. Gingrey, for 5 minutes for questions.

Mr. GINGREY. Mr. Chairman, thank you.

Dr. Collins, in a recent meeting at NIMHD July 27, 2011, you charged the Research Centers at Minority Institutions Transitional Research Network, RTRN, with providing additional opportunities for multi-site clinical and translational research among minority and collaborating institutions. What will be the proactive strategy of the National Center for Advancing Translational Science, NCATS, and NIH to collaborate and enhance the capability of RTRN to accelerate its missions to address health disparities? I know that is a mouthful, and I am sure you followed that. I will be glad to repeat if you would like for me to do that.

Mr. COLLINS. No, I think I get the gist of it. Thank you, Dr. Gingrey.

Clearly, they need to work intensively on health disparities is one of our most challenging and most important missions, and we have in fact over the years identified institutions that are particularly well designed to do so, and we have an entire institute at NIH, the National Institute for Minority Health and Health Disparities, with that focus. We just last week held a meeting of my advisory committee where I asked a very high-level group to focus on this whole question of diversity in our workforce, which is another component of this, and they made a number of very strong recommendations about what we should be doing in order to increase the numbers of individuals who work in medical research who themselves come from underrepresented groups. Oftentimes

those individuals have special interest in health disparities and oftentimes are our best researchers in those areas.

So there is a great deal of interest in promoting this through various programs through NIMHD, through the RCMI program, and I am certainly strongly in support of all of those individuals because I do think we have not much as much progress as we should in dealing with the fact that not all populations enjoy the same health as all others and one of the ways that we in research can identify the causes and interventions.

Mr. GINGREY. Dr. Collins, for that answer. Of course, we need to see a return on investments for taxpayers' dollars, especially in areas that impact so many Americans, and one costly disease that estimates are impact 26 million Americans is diabetes. Medical costs of Americans with diabetes are more than twice those without the disease. So in light of these rather startling but accurate figures, I recently shared my support for the Special Diabetes Program in a letter circulated by my colleagues, Representatives Whitfield and DeGette. Can you share with the committee the return on investment of this program and how is it helping Americans burdened by diabetes?

Mr. COLLINS. I appreciate the question. I agree with you, this is an urgent matter for our country. Not only are there those 20-some million individuals with diabetes, there are about 70 million with pre-diabetes who if nothing is done are likely to become diabetic in the not-too-distant future. This is a very high priority for research.

[Medical incident in hearing room.]

Mr. COLLINS. Coming back to diabetes. Did we lose Dr. Gingrey?

Mr. PITTS. Dr. Gingrey has gone out with the patient so he will have to follow up in writing.

Mr. COLLINS. I would be happy to follow up for the record.

Mr. PITTS. At this time we will yield to the ranking emeritus, Mr. Dingell, for 5 minutes for questions.

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy.

Good morning, Doctor. I would like to begin by asking this question. Would you please submit for the record information regarding the proposed merger of NIDA and NIAA? And I would hope that you would give us the premises under which the budget neutrality of the combining of these two institutes was established.

Mr. COLLINS. I would be happy to submit that for the record.

Mr. DINGELL. Thank you, Doctor.

Now, do you believe that NIH has lost purchasing power over the years due to inflation and that this now impairs the ability of your employees and grantees to do good science? Yes or no.

Mr. COLLINS. In my professional judgment, sir, yes.

Mr. DINGELL. Doctor, while I recognize that all of China's biomedical research is funded by the government and that the United States has the advantage of government and private-sector funding, which is critical to creativity and innovation, it is notable that China is significantly increasing its spending on scientific research and the state-of-the-art facilities. Is it fair to say that at this rate, Chinese may outspend us in biomedical research in the foreseeable future? Yes or no.

Mr. COLLINS. Yes, it is fair to say that, sir.

Mr. DINGELL. Now, Doctor, do you think that the loss of American research dominance could lead to a decrease in investment dollars and jobs in our scientific arena? Yes or no.

Mr. COLLINS. In the sense that clearly NIH research supports jobs, about seven jobs for every grant, yes.

Mr. DINGELL. Thank you, Doctor.

Now, the University of Michigan, with which I am sure you are familiar, is the largest research institution in my district, and I know you have roots back in Ann Arbor, and I am sure you agree that this brings a lot of promising young constituent scientists into my office and into Washington. Many of them share with me their fears and frustrations about how difficult it is to get good science funded properly and to generate a sustainable career. Previously, NIH was able to fund 30 percent of new grant applications. Today, the number has decreased to 17 percent. Do you believe this dearth of funding will drive the students the Federal Government has invested in away from research?

Mr. COLLINS. So those same individuals come to see me after they come to see you, and yes, they are deeply concerned and some of them are being driven away.

Mr. DINGELL. Thank you, Doctor.

Now, finally, understanding how NIH sets its research priorities, it is important to us here in the Congress and to patients throughout the country. As Members of Congress, we get inundated by advocacy groups requesting more NIH resources dedicated to their own particular disease or disease concerns and to support the legislation which would move research in their disease forward. While the suffering and frustration that is here is not easily cured, I also recognize that allocating funding based on which advocacy groups have the most presence on the Hill hurts other diseases such as rare diseases. Is this an accurate statement? Yes or no.

Mr. COLLINS. With great sympathy for those advocacy groups, it is a risk of having one battle against the other. We would be better to support all of those.

Mr. DINGELL. Thank you, Doctor.

Now, Mr. Chairman, I want to thank you for holding this important hearing. As this Congress knows, science, technology, engineering and math are the future of this country's economy, and we have to be at the cutting edge of all. Both parties, Democrats and Republicans, acknowledge the importance of working steadfastly to promote the training of our youth in these fields in order to secure our title as the world's leader in innovation and to bring the blessings that come with that kind of activity.

Today, the National Institutes of Health is the premier biomedical research institution in the whole world dedicating to promoting the public's health and wellbeing through research. The NIH has also had the foresight to recognize that cutting-edge advances in areas such as biology with the forefront of technology is where the next generation of life-altering advances will come from. So it is easy to see then how NIH's ability to be competitive in worldwide research is not only critical to our citizens but also to our economy, and I worry that the United States may be losing its competitive edge and that countries like China may be taking away the jobs and the future of our young people.

So Dr. Collins, I appreciate your assistance here, your presence today, and Mr. Chairman, I thank you for your kindness in this matter.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentlelady, Ms. McMorris Rodgers, 5 minutes for questions.

Mrs. MCMORRIS RODGERS. I thank the chairman, and I want to thank Dr. Collins for coming today, and I echo the comments and just so appreciate your leadership at NIH and everything that you are doing. I appreciated your testimony this morning.

I had the opportunity recently to meet with Dr. Chris Austin from NCATS and was very excited to learn about NCATS and particularly one pilot project, the Discovering New Therapeutic Uses for Existing Molecules Program, and I understand that this program will bridge the, quote, valley of death, that we hear so much about during the FDA reauthorization process.

I wanted to ask, do you think that this kind of an expansion of a role at NIH is going to improve NIH and better reflect the health care needs in our country, given that some are suggesting that this kind of an expansion of mission from medical research to drug development may be beyond what NIH should be doing?

Mr. COLLINS. Well, I understand the concern, and certainly, when NCATS was first being rolled out, there was a lot of misunderstanding about what its goals really were. I asked a distinguished group of experts from the private sector, people like Moncef Slaoui of GSK, Marc Tessier-Lavigne recently of Genentech, Brook Byers, venture capital expert, to look at the NCATS potential and advise me about whether this really made sense in terms of advancing the cause of developing new therapeutics in a fashion that built on NIH's sweet spots and was not sort of a deviation from what our mission should be. They started out intensely quizical and ended up wildly enthusiastic, and I would be glad to share their report with this committee.

That certainly encourages the conclusion that we are moving in a place that science now allows us to do in a partnership with the private sector to make sure that we are collaborating effectively, but with the main goal of speeding up this development of therapeutics. This is not, however, going to detract from our basic science engine, which is, of course, the critical way in which we develop new ideas for treatments of the future. That will remain about 50 percent or 51 percent of what we do. It is mostly reorganizing capabilities that we had, and you learned about some of those from Dr. Austin, into a more effective engine for doing this kind of discovery focused on the bottlenecks.

Mrs. MCMORRIS RODGERS. Well, it seems like a commonsense approach in starting to break down some of the silos that so often are difficult for us.

On another vein, I know that you are aware of the specific biologic link between Down syndrome, that duplicate 21st chromosome, and Alzheimer's disease. I am also aware that people with Down syndrome appear to have a protection from the development of some types of cancer, and this seems to be a population from which many researchers could learn many things, not only that would help people with Down syndrome but to help the general

public, and I wanted to ask what other efforts do you see as a catalyst for improving collaboration between scientists and institutions?

Mr. COLLINS. Well, I do agree that Down syndrome is an important model for understanding a variety of things that you mentioned, the Alzheimer's risk, which we believe comes about because on that 21st chromosome is the gene for beta amyloid and it is amyloid that builds up in the brain of individuals with Alzheimer's, and Down syndrome individuals have extra amounts of it because of that extra chromosome. The fact that there is a protection against cancer has recently come to light and is certainly intriguing, suggesting that we could learn something there as well.

I know you have spoken with Dr. Guttmacher, who is the Director of the National Institute of Child Health and Human Development, and he has now recently formed a Down syndrome consortium bringing together NIH and a variety of other organizations to focus on such things as, should there be a Down syndrome registry to be able to be sure that we have the maximum opportunity to collect that kind of data and even to offer clinical trial participation in a broader way, and I am excited to see where that goes. I am trained as a geneticist myself. Certainly, Down syndrome has taught us much and we owe those individuals and their families everything we can in terms of understanding how that extra chromosome results in all the consequences that it does. So it is an area of great, intense current interest.

Mrs. MCMORRIS RODGERS. Thank you, and much potential.

I am going to yield back the balance of my time.

Mr. PITTS. The Chair thanks the gentlelady and recognizes the gentleman from New York, Mr. Towns, 5 minutes for questions.

Mr. TOWNS. Thank you very much, Mr. Chairman, and thank you for this hearing, and thank you very much, Dr. Collins, for coming.

My question, Dr. Collins, is, according to the most recently available data in an area that I represent, Brooklyn, 72,000 children in Brooklyn suffer from asthma, and I know the disease disproportionately impacts children in high-poverty neighborhoods, but there is a pocket of middle class, and of course, the superintendent of the school indicated that a third of the kids in that school that reside in that area that have missed 50 days or more of school because of asthma, and they have not been able to determine in terms of what is really going on in that area. Is there any kind of special grants that you could have to look at a situation like that?

Mr. COLLINS. Well, I appreciate the question and I certainly agree that asthma is a cause of great concern, and NIH has major programs focused on research in this condition, primarily through the National Heart, Lung and Blood Institute. And asthma has been increasing in its frequency in children and certainly that is also somewhat of a puzzle. Clearly, asthma is a classic example of a genetic-environment interaction. We know it runs in families. I had severe asthma as a child, as did two of my brothers, and yet it is not sufficient to have the genetic risk, there are triggers, and we think that some of those that we know about are animal hair and feathers and house dust mites, which is a big part of this.

But to actually develop better interventions is a big part of what we are now trying to do, and it does seem that one of the things,

Mr. Towns, that we have to understand better is to how to break this disease which we just call asthma into subsets that are actually different in terms of their natural history, in terms of their response to therapy, and try to see whether within that disease are actually 10 different diseases that if we understood them better, we would realize how to personalize the approach to prevention and treatment, and that is one of the things that is making some progress, in part built upon genetics because we are understanding now what some of those risk factors are and which kids have risk factor may in fact have a lot to do with their response to treatment.

But we have a ways to go. Clearly, this is an area that in terms of pediatrics, the Child Health Institute, also intends interest in. We are running a number of clinical trials to try to test out new approaches. It is right in that space of needing to encourage translation that we have been talking about this morning.

Mr. TOWNS. Right. I know that the former chairman of the committee mentioned the merger. Have you looked at the merger from a cost analysis? Have you done that already?

Mr. COLLINS. You are talking about the merger between the Drug Abuse Institute and the Alcohol Institute?

Mr. TOWNS. That is correct.

Mr. COLLINS. Basically, what we are doing is thinking about how we could best support the science of addiction by bringing together grants that are funded through these two institutes and putting them under one roof. There was no expectation here of a shrinkage or an expansion of the overall portfolio but a rearrangement of the way in which they are overseen. So the costs should essentially not be changed more than a small amount based on simply perhaps a small amount of administrative savings from having one institute instead of two, although I really wouldn't want to emphasize that as being particularly significant because almost all of our budget goes into the grant portfolio, and we would not expect that to change.

Mr. TOWNS. And so research funding will not be impacted by this?

Mr. COLLINS. It will not. The overall research funding envelope for addiction research will remain in the same place. Now, it may be that over the course of time, science will drive that in certain directions so that some parts of addiction research will get more attention than others. That is the nature of our business but we won't keep that total support for addiction research on the same path that it has been on.

Mr. TOWNS. My time is almost expired. Let me ask, back to asthma again, is there any areas in the country where you have seen this where it is the middle class or an area where you have this high asthma rate?

Mr. COLLINS. Absolutely, and, you know, there is a theory. In fact, there is a piece about it today in the Times that one of the problems that we have in some environments is that our efforts to make the environment squeaky clean has actually increased the likelihood of asthma, that in the old days when children were exposed to lost of different kinds of dirt substances or infectious disease substances early in their life, they learned how to deal with that, and in some way we protected kids against that kind of expo-

sure. Their immune systems haven't gotten revved up when they were supposed to so they get over-revved up later on. There is a fair amount of support for that theory, and that may apply particularly in circumstances where there are a lot of resources in the family and a lot of attention to having everything spic and span.

Mr. TOWNS. Thank you very much, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentleman from Louisiana, Dr. Cassidy, 5 minutes for questioning.

Mr. CASSIDY. Hey, Dr. Collins. Thank you for being here.

There is an article by Gillum, first author, NIH funding levels and burden of disease. It relates to the interval between 1996 and 2006, and not your watch, but still, and it speaks about how in 1996, only about 39 percent of the variance between what a disease, if you will, is funded relative to its disability associated life years, etc., was explained by objective factors. And actually, between 1996 and 2006, that actually declined from like 39 percent to 33 percent. On your watch, can you tell us if there is now a better correlation between how diseases are funded relative to their impact upon mortality, morbidity, disability, etc.? Because I am looking at your Web site. It is very difficult for me to figure out if that is the case or not.

Mr. COLLINS. Thank you for the question, Dr. Cassidy. Certainly, one of the things the Reform Act gave us the opportunity to do was to form a new division, a division that has as part of its mandate doing portfolio analysis systematically across the entire NIH, trying to identify whether we have a reasonable match between public health needs and our own investments in research, and we now have more tools to do that certainly than they did in 2006, especially now that all of our grants are online and you can compute on them and see what they are actually covering. So we are looking at that with more capability and more intensity.

Mr. CASSIDY. Now, can I interrupt just for a second because time is so limited? I apologize.

Mr. COLLINS. Yes.

Mr. CASSIDY. When I look at the funding back in 2006 where, for example, AIDS/HIV, particularly if you add pediatric HIV, incredibly important disease, is getting more than ischemic heart disease, even though ischemic heart disease is the leading cause of death, and obesity, which you mentioned in your written testimony as being so important, affecting 30 percent of our population, is, I think, 40th in terms of the ranking of your priorities as you have it listed. Now, there is some double counting so maybe it is higher, but it is like, I think, \$800 million a year versus \$2.5 billion. So it seems, since that was also in 1996 and 2006 its relative ranking, has there really been that much change?

Mr. COLLINS. There has probably been a little, but let me say, I think one needs to be careful not to have this kind of analysis based on dailies being the sole way in which decisions are made about research opportunity. In addition to public health needs, there are circumstances where science provides lots of opportunity for things to go quickly and others where simply throwing the money at the problem there is no great new idea—

Mr. CASSIDY. But there is no way to know that previously, right? There is going to be a paradigm shift and so suddenly it would seem like throwing money is opening a door.

Mr. COLLINS. Well, right. So there is a connection there. That analysis, by the way, seemed to indicate that Alzheimer's disease actually was getting the kind of support that maybe it should, and I think I—

Mr. CASSIDY. No, no, no. What I see on Alzheimer's disease when I just looked at it, and again, you mentioned that in your written testimony, it is really way down there in its funding. I had it written down someplace but in my mess I can't tell, but I was struck how low the funding is relative to its potential burden.

Mr. COLLINS. In that regard, as you know, and this may come up in other speakers, certainly Alzheimer's has emerged as a scientific opportunity in the last few years and everybody would agree is a major public health initiative so we have made significant new investments in the current fiscal year of an additional \$50 million for Alzheimer's.

Mr. CASSIDY. But relative to its overall burden, \$50 million is nice in an absolute number. Man, I wish I had \$50 million. On the other hand, relative to your overall funding, again, I am struck that HIV/AIDS has remained at the top, \$2.5 billion, and then ischemic heart disease is here, obesity is there and Alzheimer's really here. So in terms of an absolutely amount, that is a lot, but in terms of its future burden to our society, it almost seems miniscule.

So let me ask you, how often do your councils actually redirect funding?

Mr. COLLINS. That is their job, so—

Mr. CASSIDY. But do they do it?

Mr. COLLINS (continuing). Every time the council meets, they look at the grants that are in front of them. They decide what new requests for applications to approve. That is their job.

Mr. CASSIDY. But how often do they do that?

Mr. COLLINS. Oh, the NIH councils are looking at new requests for applications which steer money in a new direction every—

Mr. CASSIDY. So if I were to look at your funding over time, I could see between these different categories that there would be a significant shift between funding levels?

Mr. COLLINS. You would see some shift. Again, it would not be driven by daily. It would be driven also by scientific opportunities, and some of those don't match, as we just said a minute ago.

Mr. CASSIDY. But if the correlation was 33 percent in 2006, is that correlation better now—do you follow what I am saying—with disease burden, etc.? Because scientific opportunity is frankly inertia to a certain extent. This is what we have always funded. They have got a lab set up and we are going to continue a grant. It may be—I am out of time, we have got to vote, but I will submit that for the record. Thank you.

Mr. COLLINS. Thank you very much.

Mr. PITTS. The Chair thanks the gentleman.

We are being called to vote on the floor with 20 votes and a motion to recommit that is going to go a while. Dr. Collins has other commitments. So I would suggest that we go to at least 1 minute

per member so everyone can get an opportunity to ask questions. If that OK, we will go to Mr. Lance from New Jersey, 1 minute for questions.

Mr. LANCE. Thank you, Mr. Chairman.

Thank you, Dr. Collins, for your enormous service to the Nation and I look forward to working with you on the pancreatic cancer issue.

I recently was made aware of a June 2011 article that you wrote entitled "Mining for Therapeutic Gold," and I was interested that you mentioned the need for incentives for further development and commercialization and the importance of intellectual property considerations. Sir, would you please elaborate on the challenges that intellectual-property considerations present?

Mr. COLLINS. Very briefly, I would like to see intellectual property used in a way that I think Ben Franklin intended, which is as an incentive for commercial development. When it is used in that way, it benefits everybody, the public. When it is used prematurely to claim intellectual property on information that really should be in the public domain, then it can actually have a counter-active effect.

Mr. LANCE. Thank you very much.

Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman and goes to Mr. Latta from Ohio for 1 minute for questions.

Mr. LATTI. Thank you, Mr. Chairman. Since Dr. Gingrey had to render assistance, I yield my minute to him.

Mr. GINGREY. Mr. Chairman, I sincerely thank the gentleman from Ohio, and Mr. Chairman, I thank you also. I know that I was in the midst of asking a question of Dr. Collins in regards to the Special Diabetes Program, and I was informed that you will respond, Dr. Collins, to that question in a written format.

Let me just take the remaining seconds of the minute that my friend from Ohio has yielded to me to thank you, Dr. Collins, for responding to the minor medical emergency that occurred. The young lady is fine. But I think it should reassure every member of this committee of the quality and character of our witness today, and you can find that out by reading his bio. I did. We have a lot in common, that chemistry degree you got and of course went on and got an advanced degree in physical chemistry, but when you finally took a biochemistry course, you decided you wanted to become a physician. I took that first physical chemistry course and made a D in it, and I knew immediately that I wanted to become a physician. So we have a lot in common. I just thank you for your compassion and kindness of responding to the medical emergency. Thank you, Dr. Collins.

Mr. COLLINS. Thank you, Doctor.

Mr. PITTS. I thank the gentleman and yields to Dr. Murphy from Pennsylvania 1 minute.

Mr. MURPHY. Dr. Collins, recently when we met, I had asked you how much is spent in NIH grants on overhead and indirect costs. You said it ranges from 60 to 90 percent. I believe most universities are around 50 percent. I understand indirect cost rates for private research funded by the Leukemia and Lymphoma Society is 25 percent, Juvenile Diabetes Research Foundation is 20 per-

cent. Bruce Alberts of the University of California at San Francisco said schools' reliance on the NIH to pay not only the salaries of scientists but also the overhead or indirect costs of building and construction and maintenance is a perverse incentive that encourages U.S. universities, medical centers and other research institutions to expand their research capacities.

In 2006, Yale University with an endowment of \$18 billion received \$348 million in Federal research grants. Their own spending in the university for research was \$29 million. Stanford University with an endowment of \$14 billion received \$540 million in Federal research funds and only spent \$40 million of its own money for research. MIT with an endowment of \$10.5 billion, \$476 million in Federal research funds, spent only \$10 million of its own money. Excuse me. Their endowment was \$8.3 billion. Harvard University, a \$40 billion endowment, larger than the NIH budget, they spend zero of their own dollars on research but they have 75 percent overhead costs. Can you justify this for the U.S. taxpayers and other researchers who cannot get funding for pancreatic cancer, cystic fibrosis, mitochondrial disease why you do it this way when these universities aren't spending their own money?

Mr. COLLINS. I know I have very little time. Again, NIH does not set the indirect-cost rates of those—

Mr. MURPHY. But other places can do it for 20 or 25 percent over it. I recognize this is a huge question. As an adjunct associate professor at the University of Pittsburgh, which is a recipient of a lot of NIH funding, I hope we can talk more about this because it deeply concerns us to have money available. The answer is not just to raise taxes. But I really hope that is something we can work more with you on to find solutions.

Mr. COLLINS. I would be happy to do that.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentlelady, Ms. Myrick, for 1 minute for questions.

Mrs. MYRICK. Thank you, Mr. Chairman. Thank you for being here, Dr. Collins.

I am sure that you believe holding the integrity of the peer review process is very important not only because of scientific reasons but also because of the taxpayer dollars spent. I have a question about conflict of interest at NIH relative to the selection of scientific review groups and study sections. Just looking at this one list of chair members of a particular behavioral science group, it looks like several of the individuals are serving or have served received grants while they were actually serving on the board who determines who gets the grants, and, you know, a couple of them, one of them was meth addicts to take their medicine, that kind of thing. So my question really is, does that not run counter to the conflict of interest and would you—I know our time is short but could you get back to me in writing? And then I have got a couple others I would like to submit to you.

Mr. COLLINS. I would be happy to get back to you. We have, I think, very careful methods in place to try to avoid that kind of conflict so somebody in that position would not have their grant reviewed by that same—

Mrs. MYRICK. Well, this particular one says that they actually did receive the grant, so I will get it to you. Thank you.

Mr. PITTS. The Chair thanks the gentlelady and goes to Mr. Bilbray for 1 minute for questions.

Mr. BILBRAY. Doctor, what percentage of NIH's research goes right from the researchers to the consumers and medical service?

Mr. COLLINS. You mean direct clinical application?

Mr. BILBRAY. Right.

Mr. COLLINS. I would say a rather small proportion because generally it has to go through commercialization.

Mr. BILBRAY. What percentage of your research goes through the private sector commercialization?

Mr. COLLINS. The vast majority.

Mr. BILBRAY. Give us a percentage.

Mr. COLLINS. Again, 51 percent of our budget is basic research, which doesn't have a specific commercial connection when it is being done, although it may ultimately—

Mr. BILBRAY. But it is fair to say an essential component of getting your research to the patient is the private-sector involvement in the transition from basic research to practical application?

Mr. COLLINS. Absolutely, and a central component of their success is our providing them with that information.

Mr. BILBRAY. Are you aware there are some people in that field of venture capital for medical research that have indicated that we could have in the last few years lost almost 50 percent of venture capital that builds that bridge between your research and the patients who need the breakthroughs?

Mr. COLLINS. There has been a serious stress on that system for sure.

Mr. BILBRAY. I have been informed that because of the valley of death not being closed and other regulatory issues that there is a possibility we could lose a half of what exists of what is left over. What kind of impact will that have in this country if we don't have that private-sector investment to be able to bridge that gap between your research and the patients?

Mr. COLLINS. Well, it would be devastating. We need that partnership.

Mr. BILBRAY. Mr. Chairman, I appreciate that. I would just like to point out, Mr. Chairman, that it has been estimated we have 1.4 to 2 trillion of American dollars overseas, and one of the things that my research people said that maybe Democrats and Republicans could get together and say look, if you put your foreign capital into medical research here in the United States, that both sides of the aisle should agree not to take 35 percent of that in Federal taxes but to basically focus it to bridging this gap, and I yield back, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman and recognizes the gentleman, Mr. Markey, 1 minute for questions.

Mr. MARKEY. Thank you, Mr. Chairman, very much.

Dr. Collins, if sequestration goes into effect on January 1st of next year and across-the-board cuts occur, will there be reductions in research for Alzheimer's at NIH in terms of the grants?

Mr. COLLINS. Absolutely, as well as reductions in virtually all the fields that we support.

Mr. MARKEY. So just as we recognize that we spent \$140 billion in Medicare and Medicaid last year on Alzheimer's patients, we would begin to reduce the research for the cure for Alzheimer's?

Mr. COLLINS. With \$2.4 billion being removed from the budget, there would be no way to actually spare any field of medical research from at least degree of cut.

Mr. MARKEY. Oh, my goodness. Oh, my goodness. That would be tragic.

Thank you, Doctor. Thank you for your good work.

Mr. PITTS. The Chair thanks the gentleman.

I am sorry we have been interrupted by Floor votes. This is an excellent hearing.

We will urge the members to follow up with questions in writing to you. I remind the members that they have 10 business days to submit the questions for the record, and ask if you would please respond to the questions promptly.

Thank you very much, Dr. Collins, for your excellent testimony and answers to our questions.

Members should submit their questions by the close of business Friday, July 6th. Without objection, the subcommittee is adjourned.

[Whereupon, at 1:50 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

**Opening Statement
Chairman Fred Upton
Subcommittee on Health
Hearing on the NIH – A Review of Its Reforms, Priorities, and
Progress
June 21, 2012**

(As Submitted for the Record)

On behalf of the House Energy and Commerce Committee, I would like to welcome Dr. Collins and thank you for coming here today to discuss the National Institutes of Health. The advancement of science and research is absolutely critical and translates into better outcomes for patients. NIH is a vital institution and continues to be at the forefront of medical discoveries in the US and around the world.

The NIH supports research through its own scientists and via grants on a wide variety of issues, including basic biomedical science, behavioral science, and specific diseases and conditions. Many members, including myself, are curious to hear how NIH determines its research priorities and why some diseases receive significant attention and funding while others don't seem to be on the NIH's radar. Or, how NIH selects topics in behavioral research and whether these topics reflect the best science and common values.

For example, finding hope for those who suffer from rare diseases is a priority for the Subcommittee and especially for the families who care for children with rare diseases. Creating research consortia is a way to focus on these diseases, such as Spinal Muscular Atrophy (SMA), that is the leading genetic cause of death in infants and toddlers.

The NIH has also undergone some major changes in recent years. I look forward to hearing Dr. Collins thoughts on what has worked for the agency, what needs further thought, and how Congress can best help.

Rep. Anna G. Eshoo

Energy and Commerce Committee, Health Subcommittee Hearing

National Institutes of Health—A Review of Its Reforms, Priorities, and Progress

June 21, 2012

Mr. Chairman, thank you for holding this hearing today. I want to focus on the importance of pancreatic cancer research and the need for new diagnostic tools and treatments for this devastating disease.

The statistics around pancreatic cancer are staggering—pancreatic cancer has a five-year survival rate of just 6 percent and it is the fourth leading cause of cancer death in the U.S. It is the only major cancer to have a five-year survival rate in the single digits...meanwhile the five-year survival rate for all cancers is 67%.

Since the National Cancer Act was passed over forty years ago, we've had virtually no change in the survival rates for pancreatic cancer. We need to change this.

While funding for pancreatic cancer research has increased over the last decade, it still hovers around just 2 percent of the National Cancer Institute's (NCI) budget. History has shown that when NIH identifies a research priority, it stimulates scientific interest, and that, in turn, leads to the development of better diagnostic tools and better treatments. We've seen this happen with prostate cancer, breast cancer, and HIV/AIDS.

It's time to bring the full strength and power of the NIH's resources and our best medical minds to eliminating pancreatic cancer. My colleague from New Jersey, Representative Leonard Lance, and I have introduced H.R. 733, the Pancreatic Cancer Research and Education Act to address this devastating disease. It directs NCI to develop and execute a long-term strategic plan, one that identifies specific research goals and sets benchmarks against which scientists can measure progress.

More than half the Members of the Energy and Commerce Committee have sponsored the Pancreatic Cancer Research and Education Act. More than half of the whole House, and half of the Senate have also. We have requested a CBO score of the bill and are awaiting a response.

Chairman Upton, I urge you to recognize the will of our colleagues and move the Pancreatic Cancer Research and Education Act to the floor for a vote.

NIH Director Collins Questions for the Record
House Energy and Commerce Subcommittee on Health
June 21, 2012

The Honorable Joseph R. Pitts

Question 1. The NIH and NCI accounting systems, including Research, Condition, and Disease Categorization Process (RCDC), NIH RePORTER, and NIH Guides for Grants and Contracts, combine radiation oncology and diagnostic radiology grants. Unfortunately, radiation oncology and diagnostic radiology are often confused, and the current accounting system only exacerbates this problem. As you know, diagnostic radiology uses a low-dose of radiation to view inside the body, while radiation oncology uses targeted high doses of radiation to kill cancerous tumors. I believe it would help NIH better target research funds, assist the research community and ultimately benefit patients if these two fields were accounted for separately by NIH and NCI. To help improve transparency in the NIH appropriations process and ensure that these different scientific fields and treatment areas are given the proper focus by the agency, I would like NIH and NCI to change its systems so that radiation oncology is considered separately as its own individual grant category. Please report to the Committee on whether any barriers exist in making this change and how quickly this change can be implemented. This information will help improve transparency in the NIH appropriations process and ensure that these different scientific fields and treatment areas are given the proper focus by the agency.

Answer: Thank you for bringing our attention to the issue in which radiation oncology and diagnostic radiology are sometimes confused, since the RCDC reporting system currently only includes diagnostic radiology. We agree that NIH could split these two into distinct research categories within RCDC. There are no insurmountable scientific barriers to create new categories in RCDC.¹ For Fiscal Year (FY) 2012 projects, it is too late in the fiscal year to make changes. We could implement the new categories in the future contingent upon approval through the standard process. Expanding the NIH research categorization system is very staff resource intensive, especially the initial category development stage. Regardless of whether the RCDC system is modified next year, NIH remains committed to maintaining high quality research portfolios in the fields of both radiation oncology and diagnostic radiology.

Question 2: Small businesses receive only about 2.8 percent of NIH funding (4.3 percent of funding from all federal agencies). Academic institutions are awarded over 97 percent of NIH's funding. While academic research often serves as a foundation for commercial products, the true costs and risks of bringing biomedical products to market are overwhelmingly borne by companies. This reality is not reflected in the current NIH funding. Can you discuss the role of Small Business Innovation Research at NIH and why there is an imbalance between Academic and SBIR funding?

Answer: Biomedical research can be characterized as a pipeline that spans from the laboratory to clinical trials and finally commercialization. The discoveries made in early stage research for which NIH is the leading supporter, advance our understanding of diseases and conditions and produce knowledge that is applied in later stage research. NIH invests significantly in early stage research that is typically years away from commercial viability and is often conducted in laboratories at universities and other research institutions, including small businesses. The private sector tends to invest in later stage research as products and treatments advance through the regulatory and commercialization process. It is at this point where small businesses and pharmaceutical firms play the larger role.

¹ The process for doing so can be found at <http://report.nih.gov/rcdc/process.aspx>.

The Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs created by Congress serve an important role in NIH's mission by funding small business efforts to advance commercially viable biomedical and biobehavioral technology in the early stages of development. The SBIR program's goals are to use small businesses to stimulate technological innovation, strengthen the role of small business in meeting Federal research and development (R&D) needs, increase private sector commercialization of innovations developed through Federal SBIR R&D by increasing small business participation in Federal Research/R&D, and foster and encourage participation by socially and economically disadvantaged small business concerns and women-owned business concerns in the SBIR program.

In addition, Federal agencies with extramural R&D budgets over \$1 billion are required to administer STTR programs. The SBIR and STTR programs both seek to increase the participation of small businesses in Federal R&D and to increase the private sector's commercialization of technology developed through Federal R&D. The STTR program differs from SBIR, because it requires the small business to join with a nonprofit organization to complete the project.

Congress sets the SBIR and STTR funding levels for NIH and all other Federal agencies and recently increased these set-aside percentages. Currently, the SBIR FY 2012 set-aside is 2.6 percent and the STTR FY 2012 set-aside is 0.35 percent. Small businesses must typically secure third party follow-on funding and/or partner with other organizations (pharmaceutical companies, manufacturers, and other strategic partners) to bring products to the market, since the cost involved is far beyond the amount NIH can provide in the SBIR and STTR programs.

In addition to the SBIR and STTR set-aside programs, small businesses are eligible to apply for grants from other NIH research grant programs, including NIH's Research Project Grants (R01) and Exploratory/Developmental Grants (R21), either directly or as collaborators with academic institutions.

Question 3. How does NIH define success when evaluating behavioral strategies? Is sustainability considered in evaluating a behavioral change?

Answer: In evaluating behavioral strategies to improve health, NIH defines and measures success on many different levels. On one level, NIH investigators consider whether there is an alteration in intentions or attitudes toward a behavior change (*e.g.*, I want to stop smoking or I am trying to change my diet). The second involves measures of the actual behavior change (*e.g.*, increased number of steps per day or number of days without smoking). The final measure of behavior change is often the health outcome the behavior is targeting. Thus, a study of behavior maintenance for people with Type 2 diabetes may look at (1) attitudes (*e.g.*, confidence in one's ability to eat food with a low glycemic index), (2) behavior (*e.g.*, did diet and activity levels change), and (3) hemoglobin A1C as a biological marker of improved blood glucose control, presumably as a result of successful behavior change. On all of these levels, and for a broad range of health-related behaviors, generating successful behavior change requires understanding the mechanisms that play a role in initiating or maintaining behavior change. This is the primary objective of the NIH Common Fund's Science of Behavior Change program.²

Evaluating the success of behavioral strategies at improving public health and reducing the burden of disease is an important component of the NIH mission. There is strong evidence that modifiable behaviors, such as cigarette smoking, excessive alcohol consumption, illicit drug use, and physical inactivity are associated with at least half of all premature deaths in the United States each year.

² <https://commonfund.nih.gov/behaviorchange/>.

An analysis by Schroeder³ published in the *New England Journal of Medicine*⁴ argued that behavioral causes account for about 40% of all deaths in the United States¹. In contrast, only about 10% of health outcomes are attributable to medical care. The combination of over-nutrition and low levels of physical activity are the primary factors driving the epidemic in obesity and the consequent increase in type 2 diabetes, high blood pressure, and some cancers. To assess the success of behavioral interventions, NIH supports a variety of studies that use randomized clinical trial methods to ascertain whether people who have experienced a behavioral intervention are more likely to demonstrate behavior change in comparison to control groups who did not receive the intervention. A wide variety of methods are also applied in observational studies to assess behavior change. For example, studies of adherence to prescribed medications now use small microprocessors to determine whether pill bottles have been opened and can estimate adherence from the number of prescription refills. Behavioral studies include rigorous measures of behavior using assessment methods that are vetted for validity and reliability during the NIH peer review process. In some cases, the change in behavior is evaluated against long term health benefits. For example, studies have shown that changes in rates for smoking behavior at the state level are followed some years later by significant declines in rates of lung cancer and emphysema.

Sustainability is considered in many studies evaluating behavior change. In fact, sustainability of interventions, including those designed to change health behaviors, is increasingly recognized as an important focus of research. The NIH supports research on sustainability at multiple levels, including behavior at the individual level, the extent to which components of behavior change strategies are implemented at an organizational level, and the capacity to deliver behavior change programs at a community level. The topic of sustainability is supported through multiple NIH funding opportunity announcements. From 2003 to 2008, NIH's Office of Behavioral and Social Sciences Research in collaboration with NIH Institutes and Centers supported an initiative in which a number of studies on maintenance of behavior change were funded. This important issue continues to be supported collaboratively through the Basic Behavioral & Social Science Opportunity Network Mechanisms of Behavior Maintenance initiative as well as through projects funded through individual Institutes and Centers. NIH will continue to support research targeting all of the important levels described above for the establishment of sustainable long-term behavior change to prevent disease and improve health.

Question 4: How does NIH ensure that there is no conflict of interest with the grant reviewers?

Answer: NIH has multiple protections in place to ensure that conflicts of interest are minimized and managed in the peer review process. As specified in regulation 42 CFR 52h,⁵ reviewers in initial peer review are excluded from the review process for conflicts based on financial or other interests. These include direct financial benefit of any amount deriving from an application or proposal under review, and financial benefit from the applicant institution, offeror, or principal investigator that in the aggregate exceeds \$10,000 per year.

Second, NIH policy on managing conflicts of interest in initial peer review was revised and published last year⁶ to reflect the increasingly multi-dimensional, inter-disciplinary, and collaborative nature of modern biomedical and behavioral research, and increase transparency for the peer review process. The revised policy addresses situations encountered in reviews of specific types of applications (fellowships, conference grants, etc.) and clarifies conflict rules applicable to Federal employees who serve as reviewers in the NIH peer review process.

³ Schroeder SA. Shattuck Lecture. We can do better--improving the health of the American people. The New England journal of medicine 2007;357:1221-8.

⁴ <http://www.nejm.org/doi/full/10.1056/NEJMs073350>.

⁵ See http://grants.nih.gov/grants/policy/fed_reg_peer_rev_20040115.pdf.

⁶ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-11-120.html>

In addition, regardless of the level of financial involvement or other interest, if the reviewer feels unable to provide objective advice, she/he must recuse themselves from the review of the application or proposal at issue. The regulatory definition of conflicts of interest in initial peer review includes employment, involvement of close relatives, membership on a standing review group, or any other consideration that might lead a knowledgeable person to question the integrity of the process.

Each NIH reviewer is required to declare conflicts of interest to the NIH Scientific Review Officer managing the review, and to sign two Conflict of Interest certifications attesting that they have declared such conflicts and have recused themselves from the evaluation of any application with which they have such conflict or could appear to have such conflict. The evaluation of research and development contract proposals is governed by rules based on the Federal Acquisition Regulation. In these cases, no reviewer may be an employee of any offeror responding to the Request for Proposals.

Finally, the second level of NIH peer review involves the National Advisory Councils or Boards (NACs) of the Institutes and Centers. NAC members, who are appointed as Special Government Employees, are subject to conflicts of interest and regulatory Standards of Ethical Conduct as full-time Federal Employees. These rules generally prohibit participation in matters that would affect a personal financial interest, or the interests of certain others. Financial interests triggering recusal obligations include investment, employment, and other business relationships.

Question 5. Dr. Collins stated in a letter to Chairman Pitt's letter last year that "Governments and private institutions in other countries have helped to support the addition of content to PMC" (NIH's publicly accessible PubMed Central database). In light of the fact that two-thirds of downloads from PMC are from foreign users, it would be interesting to know if U.S. citizens are benefitting from funding efforts of any foreign governments.

Answer: One of the ways PubMed Central (PMC) benefits American citizens is by providing them with access to articles funded not only by NIH, but also by foreign governments and private research funders. PMC hosts the full-text content of almost 1,100 biomedical and life sciences journals, in addition to articles resulting from NIH-funded research. A significant number of these articles result from biomedical research funded by foreign sources, and PMC ensures that these articles are accessible to American users. The knowledge in these foreign scientific articles not only helps United States scientists build upon these results directly to make discoveries, but also assists United States science agencies to better allocate funding by avoiding duplicative efforts.

In addition, PubMed Central has established special relationships with public and private biomedical research funding agencies in Canada and the United Kingdom (U.K.) that make the results of their funded research available to United States users of PMC in a timely fashion, typically no more than a maximum of six months after publication. PMC Canada, which became operational in 2009, serves as the repository for articles funded by the Canadian Institutes of Health Research (CIHR). UK-PMC became operational in 2007 and serves as the repository for articles reporting on research funded by more than 18 funders of biomedical research, including the U.K. National Institute for Health Research, U.K. Biotechnology and Biological Sciences Research Council, U.K. Medical Research Council, Austrian Science Fund (FWF), and Wellcome Trust. The European content available to United States citizens via PMC is poised to expand following the July 13, 2012, announcement by the European Research Council (ERC) that it will participate in UK-PMC and that UK-PMC will be rebranded "Europe PubMed Central." A key aim of the Europe PMC initiative is to extend the repository further and encourage other European funders of life sciences research to make the outputs of the research they fund freely available through Europe PMC.

The Honorable Fred Upton

One of the particular challenges we face in rare disease research today occurs when non-profit organizations and small biotech companies make remarkable progress on basic and pre-clinical research but then find the cost of establishing and maintaining clinical trials is beyond their means. This is the case, for example, with spinal muscular atrophy, which has several promising therapies in early trials or approaching the clinic. Please describe for us how NIH can help bring clinical research across the finish line for rare diseases like SMA.

Answer: Because of remarkable progress in understanding rare diseases, researchers supported by NIH, non-profit organizations, biotech companies, and large pharmaceutical companies are now developing promising therapies for many neurological diseases, including spinal muscular atrophy (SMA). With therapies now approaching readiness for testing for several diseases, the National Institute of Neurological Disorders and Stroke (NINDS) devised a new approach and recently established the NeuroNEXT clinical research network. The network specifically supports early stage, phase 2, clinical trials of novel therapeutics. The first clinical research in NeuroNEXT will be a SMA biomarkers study.

NeuroNEXT has central data and clinical coordinating centers and 25 clinical sites throughout the United States, with resources and expertise far greater than could be dedicated to a single disease. By design, the network will protect intellectual property to encourage testing of the most promising candidate treatments whether they arise from foundations, industry, or academia. The network will efficiently handle regulatory and contractual issues, rapidly engage appropriate teams of researchers and clinical sites, decrease the time between trial design and execution, and reduce trial cost. As a multi-disease network, NeuroNEXT can keep resources and expertise more continuously engaged in productive research than would be possible in a single disease network. By maintaining support for clinical infrastructure and expertise, including clinical research coordinators, the network will reduce delays in building infrastructure for each new trial, improve the speed of enrollment of trial participants, foster the highest quality clinical research, and enable better choices of therapies for phase 3 clinical trials, another key issue for rare disorders such as SMA for which multiple candidate therapies are emerging. Moreover, any qualified investigators can apply to conduct a study within the network as use of the resources is not limited to those who are part of the NeuroNEXT infrastructure.

While development of NeuroNEXT was underway, NIH and the Food and Drug Administration (FDA) jointly sponsored a scientific workshop that brought together researchers and disease advocates to discuss the development of biomarkers for SMA. Biomarkers are objective measures of the disease process or the biological actions of candidate therapeutics that can expedite therapy development. Lack of validated biomarkers of disease progression, pathology or therapeutic action in phase 2 studies is a major impediment to therapy development in many diseases. NINDS followed up with a solicitation for SMA biomarkers studies and will fund an SMA biomarkers study as the first clinical research in NeuroNEXT. NINDS has also solicited clinical trials proposals from foundations, industry, and academia, and is now reviewing proposed clinical trials to be conducted by the network.

The Honorable Henry Waxman

The NIH Scientific Management Review Board (SMRB) has recommended a reorganization of addiction-related activities at NIH. As I understand it, the proposal would consolidate the substance use, abuse, and addiction research within the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and other NIH institutes and centers into one, new entity.

Question 1. I believe you have endorsed the SMRB reorganization recommendation. Please summarize why you and the SMRB believe this reorganization will advance research in the field of substance use, abuse, and addiction.

Answer: We will work with the Committee to address your concerns.

Question 2. What kinds of addiction-related research – other than research on drugs and alcohol – would be moved out of the existing institutes and centers into the new proposed institute? For example, would tobacco addiction research now housed at NCI be moved? What about the food addiction component of obesity – would it be included in the new institute or get moved to NIDDK? And what about research on fetal alcohol syndrome, drug addiction related to HIV/AIDS and alcohol-related liver, heart, and lung disease? What will happen with each of these research portfolios? What is the process for determining which portfolio will end up in which institute?

Answer: We will work with the Committee to address your concerns.

Question 3. In response to a question from Congressman Towns, you testified that the funding level for addiction-related research will not change as a result of the proposed merger between NIDA and NIAAA. Please provide a list of each addiction-related research portfolio – including the amount of funds for each such portfolio – that is expected to be transferred to the new institute.

Answer: We will work with the Committee to address your concerns.

Question 4. What about the administrative costs associated with the proposed merger and establishment of a new institute? They must be absorbed somewhere in the NIH overall budget. Will these costs be covered by the Office of the Director or will NIDA and NIAAA have to pick up the tab?

Answer: We will work with the Committee to address your concerns.

Question 5. How can we be assured that support for substance use, abuse, and addiction research won't be short-changed – in terms of dollars and other types of commitments – in this reorganization?

Answer: We will work with the Committee to address your concerns.

Question 6. I understand you have established a task force to look at these and other issues involved in the proposed consolidation of NIDA and NIAAA. Following the completion of the task force's review, what are the next process steps in implementing the SMRB's recommendation? What is the proposed timeframe? Will there be an opportunity for public comment? Do you intend to bring the final product to Congress to ask for legislation to codify the merger?

Answer: We will work with the Committee to address your concerns.

Question 7. There are unique research challenges for diseases such as SMA whose patient population is very fragile. Providing continuity between testing facilities is critical – even when clinical trials may be in a slight lull. I understand staffing these facilities with specialists is essential and may be difficult to accomplish on a one or two year timeline. Please explain how NIH could address this potential bottleneck for SMA clinical trials.

Answer: There are several neurological disorders for which potential therapies are now emerging, including rare and severe pediatric diseases such as spinal muscular atrophy (SMA). Providing infrastructure and expertise to rapidly test candidate treatments is essential. However, developing and maintaining separate networks for many diseases is simply not feasible, nor, for reasons you note, would these resources be productively engaged at all times because of waxing and waning opportunities. For this reason, the National Institute of Neurological Disorders and Stroke (NINDS) has developed NeuroNEXT -- a clinical network with central clinical and data coordinating centers and 25 clinical sites, including Children's Hospitals, throughout the United States that can serve multiple diseases. The first clinical research in NeuroNEXT will be a SMA biomarkers study.

Because NeuroNEXT serves multiple diseases, NINDS can dedicate far more resources and expertise, including pediatric investigators and clinical trials experts, than could be dedicated to separate networks for each disease. The network should be cost-effective as it continuously responds to new therapeutic opportunities throughout clinical neuroscience.

NINDS also designed NeuroNEXT to protect intellectual property so the network can test the best opportunities from academia, foundations, or industry. By maintaining support for clinical infrastructure and expertise, including clinical research coordinators, and efficiently addressing regulatory and contract requirements, the network will reduce delays in starting each new trial. It will also strive to improve the speed of enrollment of trial participants, foster the highest quality clinical research, and enable better choices of therapies for phase 3 clinical trials, another key issue for rare disorders such as SMA for which multiple candidate therapies are emerging.

If successful and cost-effective, NeuroNEXT is scalable to accommodate increasing the number of phase 2 trials. In addition to conducting early phase clinical trials, NeuroNEXT is conducting clinical research that will prepare for more efficient trials. For example, while development of NeuroNEXT was underway, NIH and FDA jointly sponsored a workshop in May 2011 on biomarkers for SMA, which could expedite testing of therapies by providing objective indication of disease progress and the effect of therapies. Following a subsequent solicitation for proposals, NINDS is funding a study of SMA biomarkers as the first clinical study in NeuroNEXT.

Question 8 and 9. As you know, the Cures Acceleration Network (CAN) was initially authorized in the Affordable Care Act and is now housed within NCATS. I understand the goal of this initiative is to translate promising discoveries into new, approved therapies for important diseases that have not been prioritized for development by private industry.

During your testimony, you outlined one new initiative that has come about through the Cures Network – the Discovering New Therapeutic Uses for Existing Molecules program. Please describe other CAN projects – already in existence or on the drawing board.

Answer for 8 and 9: Approximately \$9 million is being used to support the new Tissue Chips for Drug Screening program. This program will support research to develop tissue chips that can be used to predict the performance of a candidate drug, vaccine, or biologic agent quickly and inexpensively. These bio-

engineered tissue models, which are designed to mimic human physiology, will provide a new way to test candidate drugs in the tissue chips to see if they show signs of being toxic to human tissues. Additionally, the chips may help researchers determine whether compounds are binding to their intended targets and exhibiting the desired activity. By providing additional safety and toxicity information about the compounds, the chips will help researchers decide whether or not to proceed to clinical trials, saving time and money. The NIH Common Fund will also provide \$4 million for this program in FY 2012.

The FY 2013 President's Budget requests \$50 million for CAN. Funds will be used to continue to support the second year of the Tissue Chip awards, as well as to fund the awards for the Discovering New Therapeutic Uses for Existing Molecules (Therapeutics Discovery) program. The Therapeutics Discovery program was announced in May 2012, a request for applications was issued in June 2012, and, pending appropriations, awards will be made in the summer of 2013.

As requested by Congress in the Statement of Managers accompanying the Consolidated Appropriations Act of 2012, NCATS also contracted the Institute of Medicine to hold a workshop to explore ways that NCATS could use the new authorities provided by CAN. This workshop was held on June 4-5, 2012, and a summary of the workshop is expected. NCATS is considering the discussions that took place during the workshop as it determines additional opportunities to support research on high need cures.

NCATS is in the process of establishing the CAN Review Board. Members of the Board have been selected and are currently being vetted. The first meeting of the Board is expected to be in September of 2012.

The Honorable John Shimkus

Question 1. When you responded to Ranking Member Pallone that much more needs to be done to address the challenges presented by pancreatic cancer, what, specifically does NIH and NCI define as the challenges? What is the plan to overcome or address these challenges in the next year, the next five years, and beyond?

Answer: While significant strides have been made towards understanding pancreatic cancer in the past two decades, significant challenges remain. This is due, in part, to the aggressive nature of the vast majority of pancreatic cancers, the complex biology of this cancer, the lack of early screening tools, and the absence of effective targeted therapeutic agents. Pancreatic cancer is distinct from most other cancers because the tumor elicits a shell-like biological barrier around itself, limiting blood flow and making it difficult to deliver drugs to the tumor. In addition, because symptoms often do not arise until there is extensive disease, approximately half of pancreatic cancer patients are diagnosed at a late stage when the disease is inoperable or has already spread to other organs. Although the outlook is somewhat better for patients who are diagnosed with early disease, it still proves fatal to the vast majority of them.

Over 90 percent of pancreatic cancers harbor similar or identical mutations in the same gene, the K-RAS gene; moreover these mutations in K-RAS also occur frequently in tumors in other organs, including the lung and colon. However, despite more than two decades of intense work by the research community, pharmaceutical industry and the academic sector, efforts to block the effects of these mutations in the fashion achieved with other gene-targeted drugs, such as Gleevec or Herceptin, have been uniformly unsuccessful. Furthermore, the large number of additional genetic mutations involved in pancreatic cancer further complicates the development of effective targeted therapies to disable the growth of cancer cells and arrest progression of the disease.

Despite these difficulties, and thanks to improved technologies and the interest of many outstanding investigators in pancreatic cancer, the National Cancer Institute (NCI) has dramatically increased the number of grants to fund meritorious research in this area. This includes a broad spectrum of research, from improving the detection and management of this cancer to the development of relevant cell-based and animal models that enable a detailed study of the pathogenesis of this cancer and the preclinical testing of new candidate therapeutic interventions.

Important research targeted toward the genes and pathways that are de-regulated in pancreatic and other cancers is being done. For example, NCI-supported scientists are studying the presence of mutations in the K-RAS gene, to improve our understanding of the K-RAS pathway and enable the development of new therapeutic interventions to overcome its de-regulation in cancer. In another example, NCI-supported researchers recently reported that inhibition of an enzyme known as protein kinase C delta (PKCD) is toxic to pancreatic cancer cells. Since the PKCD enzyme is tumor-promoting in the presence of mutant K-RAS, it is possible that a small molecule inhibitor of PKCD could have potential as a targeted therapy for pancreatic tumors and other cancers with K-RAS mutations. While this particular study focused on pancreatic cancer cells, the researchers, based at the Boston University Cancer Center, are also exploring the basic molecular and cellular biology of various cancer types. NCI-supported research will continue to build upon these findings in an effort to determine whether PKCD inhibitors have clinical applications for pancreatic and other cancers.

Pancreatic cancer is one of the tumor types selected for analysis by The Cancer Genome Atlas (TCGA), a large-scale project jointly sponsored by the National Human Genome Research Institute (NHGRI) and NCI, where the molecular abnormalities of thousands of tumors from more than 20 different cancer types are being collected and analyzed. This research has the potential to expand our understanding of the

range and frequency of various genetic and epigenetic abnormalities in this cancer, with the longer-term goal of validating candidate molecular targets identified from this analysis and developing effective therapeutic interventions against these targets.

To ensure that NCI supports high quality research applications for common cancers that are refractory to progress, the Institute has been giving higher priority to funding highly meritorious applications that have fallen outside the current payline. In FY 2012, the NCI “selected” several applications for funding in this way. Those research programs include a study to better understand the molecular events that enable the progression of precancerous pancreatic lesions to cancer; an effort to improve the current standard of care by developing molecular imaging capabilities to optimize certain treatment therapies; work to improve molecular diagnostic analysis for disease detection and management, especially at early stages; and genetic studies to accelerate the discovery of genes that predispose families to pancreatic cancer. Of course, these “selected” awards are only additions to the large number of awards for pancreatic cancer research made through the normal process. A large sampling of these awards can be viewed in the NCI’s 2011 report on Investment in Pancreatic Cancer Research.⁷

Question 2. In light of Congressional requests to produce a long range strategic plan for pancreatic cancer research, does NIH or NCI have a written multi-year strategic and tactical plan to address pancreatic cancer? How are you communicating this plan to Congress and external stakeholder organizations? If there is no plan, why not?

Answer: The NCI’s Investment in Pancreatic Cancer Research Action Plan (FY 2011)⁸ includes progress reports on NCI’s implementation of recommendations from the 2001 Pancreatic Cancer Progress Review Group.

Additionally, in 2008, the NCI Gastrointestinal Steering Committee convened a “Clinical Trials Planning Meeting on Pancreas Cancer Treatment,” to discuss the integration of basic and clinical knowledge in the design of clinical trials in pancreatic ductal adenocarcinoma (PDAC). A Consensus Report from this meeting was published in the *Journal of Clinical Oncology* in November 2009.⁹ The committee placed major emphasis on three areas: enhancement of research to identify and validate the relevant targets and molecular pathways in PDAC, cancer stem cells, and the microenvironment. The committee also identified additional research priorities, including the development of combination therapies and predictive biomarkers. The Consensus Report has helped to guide many of NCI’s pancreatic cancer research efforts over the past three years.

Nevertheless, it is important to observe that, while we can plan ways to study pancreatic cancer with many methods at our disposal, our understanding of the disease is not yet mature enough to develop a plan for prevention, early diagnosis, and treatment. Consistent with NIH’s experience, for advances on important clinical aspects of the disease, it is important to encourage investigators to propose imaginative and technically sophisticated approaches and to fund those who are judged to have strong scientific merit. It is customary for NCI leadership, investigators in our research communities, and scientific program managers to periodically review progress toward critical goals and to “scan the horizon” for methods and ideas that could be employed to nurture future efforts. NCI is using its established Clinical and Translational Advisory Committee to oversee such reviews and “horizon scans” for several cancers, including pancreatic cancer, that have proven refractory to improvements in prevention, early detection, and treatment. The subcommittees being formed to conduct these surveys will include subject experts, Cancer Center directors, and other well-established investigators in cancer research. The intent of these

⁷ <http://www.cancer.gov/researchandfunding/reports/pancreatic-action-plan.pdf>.

⁸ *Id.*

⁹ <http://jco.ascopubs.org/content/27/33/5660.full.pdf>.

exercises will be to determine whether NCI has been employing the full range of its talents and methodologies to study such cancers, whether significant progress has occurred, and how the Institute can be more effective in pursuit of the goal of reducing the morbidity and mortality of every type of cancer.

Question 3. The strategies for advancing translational and clinical science often involve large, long-term infrastructure approaches (examples include the National Center for Advancing Translational Science (NCATS), the NIH's Clinical Center, and NCI's Cancer Center, Clinical Trials Cooperative Groups, and Specialized Programs of Research Excellence (SPORE) programs). Maintaining the peer-review system, does the NIH see value in devising and long-term strategic plan that would incentivize leveraging their investment in this infrastructure to make advances in specific diseases that have been particularly challenging, such as pancreatic cancer? If not, why not?

Answer: The Clinical and Translational Science Award (CTSA) program, supported by NCATS, provides infrastructure support to many NIH-funded research projects, increasing the efficiency and expanding the reach of NIH's disease-specific researchers. Recognizing the value that CTSA institutions bring to their research priorities, many NIH Institutes include language in their Funding Opportunity Announcements encouraging applicants to utilize the resources provided by the CTSA. For example, the National Cancer Institute (NCI) encouraged applicants to work with the CTSA institutions in the Community Networks Program – Centers for Reducing Cancer Disparities through Outreach, Research and Training.

There are many examples of collaboration between CTSA and NIH-funded cancer research:

- The Atlanta Clinical and Translational Science Institute (ACTSI) provides important support to the researchers at Winship Cancer Institute of Emory University, including nursing, laboratory, and database support. The ACTSI also helps fund pilot cancer studies and cancer research trainees to support innovative cancer studies.
- The University of Michigan CTSA, the Michigan Institute for Clinical Health Research (MICH), has worked to strengthen its collaborations with the NCI's Comprehensive Cancer Center and Specialized Programs of Research Excellence (SPORES) in ways that leverage resources and promote best practices.
- The University of Iowa's Institute for Clinical and Translational Science supports the informatics needs of a multidisciplinary team of scientists at the University of Iowa who received a five-year, \$3 million grant from NCI to develop new image analysis tools to better assess treatment response among patients with cancer. The newly developed tools have been applied to a number of prospective clinical trials.
- UCSF's Helen Diller Family Comprehensive Cancer Center,¹⁰ funded by the NCI and the CTSI Clinical Research Services program,¹¹ have joined forces to introduce novel agents for patients with incurable diseases through an early-phase clinical trials unit. This unit has the capability to efficiently screen, assess, and treat patients who can benefit from novel therapies.

Regarding your specific reference to pancreatic cancer, we note that NCI conducts much of its disease-oriented research within the NCI-designated Cancer Centers that represents the Institute's major infrastructural investment. Moreover, NCI makes substantial investments in scientific teams that conduct clinical trials, work on computation problems, or focus on specific diseases through its program project grants, its cooperative clinical trials networks, and its SPORE programs, all of which include elements that concentrate on pancreatic cancer.

¹⁰ <http://cancer.ucsf.edu/>

¹¹ <http://ctsi.ucsf.edu/about-us/programs/clinical-research-services>

Question 4. Dr. Collins: I have been a supporter for significant investment in gastric cancer research to combat this deadly cancer growing in young people in the US and I commend you for selecting gastric cancer as one of the cancers to be analyzed by TCGA. I urge you to press forward on this research to ensure numerous US diffuse gastric cancer samples are obtained and analyzed. In addition, NCI should establish a comprehensive program to guarantee the data generated by TCGA is able to be translated to assist US patients. NCI must fund research by top investigators and institutions that utilize the TCGA data to make progress in the understanding and treatment of cancer, particularly for cancers like gastric cancer where there has been so little research in the past. Dr. Collins, will you outline for the Committee your expected future outlook for TCGA and how NCI can best “cash the check” to make the very most of the significant federal investment in this area?

Answer: Historically, one of the major impediments from accruing diffuse-type gastric cancer cases into The Cancer Genome Atlas (TCGA) pipeline has been the requirement for treatment-naïve (untreated) cases. Chemotherapy changes the genomic make-up of tumors and our goal is to understand primary, sporadic tumorigenesis. Therefore, TCGA needs samples that have not been altered by treatment. However, almost all United States diffuse gastric cancer cases are uniformly pre-treated prior to surgical resection. TCGA has recently piloted a protocol that would allow it to use non-surgical specimens in our program. This means that TCGA could potentially use core-needle biopsies, which could happen as part of a diagnostic protocol, prior to treatment. This protocol has been shared with sites all over the United States, and TCGA is hopeful that this will inspire more groups to become involved. This approach is already working for esophageal cancer, a tumor type that had similar neoadjuvant treatment restrictions.

Additionally, TCGA is actively pursuing the development of a robust pipeline for samples that have not been frozen, but instead have been fixed in a formalin-based fixative and embedded in paraffin. This is the standard for most clinical pathology to date. TCGA has a set of new protocols that are being tested using materials isolated from this type of biospecimen. In anticipation of positive results, TCGA is partnering with Cancer and Leukemia Group-B (CALGB), an NCI clinical trials cooperative group, and is applying to perform gene sequencing and gene expression on samples collected from a CALGB trial organized by Dr. Charles Fuchs. This, however, remains in early stages and would not replace the goals of the network to characterize comprehensively flash frozen samples when those samples can be located.

NCI is sponsoring extensive efforts to interpret the vast findings that are emerging from the study of each tumor type; to identify genetic and epi-genetic changes that have potential for changing the way we detect, diagnose, treat, and prevent various cancers; and to conduct translational and clinical studies, such as drug development and testing, often in conjunction with industry, that would improve the control of these cancers.

The Honorable Mike Rogers

I have been a strong proponent of FDA laws to promote the study of drugs and devices in children, including the Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act, and the Pediatric Medical Device Safety and Improvement Act. I believe it is also important that children are included in and can benefit from NIH trials when appropriate. I am concerned that NIH could do a better job tracking the inclusion of children in human subjects research.

1. Is every NIH-funded investigator required to report the specific ages of those included in a particular trial?
2. Do all investigators collect date of birth on trial participants?
3. How specific is this reporting to NIH? For instance, I'd hope that including one 17-year-old in a trial wouldn't be reported in the same way as a trial containing many infants and children.

Combined Answer: NIH has had a formal policy on the inclusion of children (specifically defined as under the age of 21 years) in research involving human subjects since 1998. If investigators submit applications proposing to conduct clinical research, they must describe their plans for including children, unless the science or ethical reasons justify exclusion. The policy provides several examples of specific justifications for exclusion, such as the proposed research topic is largely irrelevant to children, or children are barred from inclusion in that research. Specifically, investigators must identify in their grant applications the age ranges of the children proposed for the study and the pediatric expertise of the research team.

The NIH inclusion of children policy does not require reporting the date of birth of trial participants. Of course, investigators do have to determine whether individuals meet studies' criteria for participation, which may require collection of date of birth. Success in recruiting within the age ranges proposed for the study would be discussed in the required annual progress reports to the NIH and evaluated by scientific program staff as part of their monitoring and oversight of the award.

In response to a request from the American Academy of Pediatrics (AAP), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) conducted an evaluation of the NIH pediatric inclusion policy for NICHD grants. The results, as presented to the AAP in 2009, showed that 87 percent of the NICHD grants reviewed included children under age 21, while 13 percent included only people of age 21 or greater. Sixty-five percent of the NICHD grants reviewed included children under age 18.

As a result of recent recommendations from an internal task force on inclusion, NIH has established a new governance body which is taking a closer look at NIH policies and overall inclusion of different populations in clinical research. This group is co-chaired by the Director of NICHD and the Acting Director of the Office of Research on Women's Health. The Subcommittee on Inclusion Governance is charged with examining and considering current NIH policies related to the inclusion of different populations in clinical research, including children. As appropriate, they will recommend to NIH leadership new or revised procedures to ensure NIH is meeting the goals of these policies and how they can help the agency achieve its mission of turning discovery into health. The leaders of this governance group and the NIH Inclusion Policy Officer are meeting with research experts from AAP to discuss additional avenues for pediatric data collection and analysis.

The Honorable Sue Myrick

Question 1. Dr. Collins: I'm sure you believe that upholding the integrity of the peer-review process at NIH is very important-- not only for scientific integrity, but also to ensure that taxpayer dollars are going to projects with the most merit. I have a question about conflict of interest rules at NIH when it comes to the selection of scientific review groups and study sections. I took a brief glance at a list of the chair and members of a particular behavioral science study group, and it certainly looks like several individuals who are serving or have served on this grant review board have actually received their own grants WHILE they were serving on the board that determines who gets grants. Some of these were grants that most Americans would probably be surprised to learn were funded with their money including studies on how to get Meth addicts to take their medicine. Doesn't this practice run counter to NIH conflict of interest rules? If not, please explain why.

Answer: The rule prohibiting a study section from evaluating the work of one of its members is set out in regulations at 42 CFR Part 52h. The National Institutes of Health adheres strictly to this rule, which states "When a peer review group meets regularly it is assumed that a relationship among individual reviewers in the group exists and that the group as a whole may not be objective about evaluating the work of one of its members. In such a case, a member's application or proposal shall be reviewed by another qualified review group to ensure that a competent and objective review is obtained."

The conflict of interest restriction applies to all applications for competing awards, which are assessed by study sections. When a study section member submits a competing grant application, including a competing renewal, it is reviewed by a different study section if the member is still serving.

When a grant application is reviewed and found to be meritorious, it usually is awarded for a project period which spans multiple years, but funds are awarded incrementally on a yearly basis; the second and later years of the grant are awarded as non-competing awards after a review of the prior years' progress by NIH staff. Study section members are not involved in the review of non-competing awards. These are reviewed administratively by scientific program staff. Conflict of interest rules do not prohibit NIH reviewers from receiving non-competing awards during their term of service to NIH study sections.

With regard to why NIH supports a study involving methamphetamine addicts, the reasons relate to the extraordinary human health and society costs of drug abuse and addiction. Chronic methamphetamine abusers can display a number of psychotic features, including paranoia, visual and auditory hallucinations, and delusions. Methamphetamine addiction has many negative health consequences, including extreme weight loss, severe dental problems, anxiety, confusion, insomnia, mood disturbances, and violent behavior. NIH research is aimed at the development of medications and new behavioral approaches as well as prevention strategies for this population.

Question 2. Congress has learned that NIH has funded projects whose subject matter and material is undignified and very graphic - even pornographic. We understand that NIH establishes criteria for the merit of a research project, particularly scientific merit. Shouldn't there be review criteria to prevent the use of federal funds on material that is pornographic or material that conflicts with rules for the Protection of Human Subjects?

Answer: The protection of participants in research is of utmost concern to NIH. A grant application that has inadequate or unacceptable plans for protecting human subjects will not receive NIH funding. First, during the peer review of grant applications, reviewers must evaluate the proposed plan for protecting human subjects by assessing five criteria: the risk to subjects from the proposed study design; adequacy of protection against risks; potential benefits to the subjects and others; the importance of the

knowledge to be gained; and, if the study involves a clinical trial, how data and safety monitoring will be conducted. Second, if the review panel deems the human subjects protections described in the application to be unacceptable, funds for the proposed human subjects research cannot be awarded until the concerns are resolved to the satisfaction of the NIH Program Officer handling the grant and of the Human Subjects Protections Officers in the Office of Extramural Research (OER).

In addition to these review considerations which occur prior to funding, nonexempt research involving human subjects may only be conducted under any award issued by the Department of Health and Human Services (HHS) if the engaged organization(s) is operating in accord with an approved Federal-Wide Assurance (FWA) and provides verification that an Institutional Review Board has reviewed and approved the proposed activity in accordance with the HHS regulations (45 CFR 46) stipulated by the HHS Office for Human Research Protections. Those regulations state, in part “Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.” Therefore, participants can only be involved in NIH funded non-exempt human subject research after they have given their specific informed consent through a process that has been reviewed, approved and is overseen by the IRB, unless an IRB has waived the requirement for informed consent.

Finally, reviewers in both levels of the NIH peer review process have multiple opportunities to identify inappropriate research in their assessment of scientific merit and suitability for funding. In the review of all applications for NIH research support, reviewers assess the significance of the proposed study, the qualifications of the investigators, level of innovation, feasibility of the approach, the research environment, and overall impact. Overall impact is defined as the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved. Therefore, if reviewers conclude that particular studies would not advance the research field involved or, in some cases may be harmful, this opinion should be reflected in the overall impact score.

Much of the success in improving the Nation's health over the past decades can be attributed to advances in our understanding of human biology. The constant battle against illness and disease, however, cannot be confined to biological factors; we must include behavioral and social factors as well. Unhealthy human behaviors have been estimated to be the proximal cause of over half of the disease burden in our country. Unhealthy human behaviors, including smoking, overeating, physical inactivity, abuse of alcohol and illicit drugs, unprotected sex, and violence, have been estimated to be the proximal cause of over half of the disease burden in our country, and they are at the core of many illnesses that public health efforts are trying to reduce and prevent.

Question 3, Part 1. Do you think that NIH should have a strategic mission to more heavily fund research for particularly deadly illnesses – whether they are pancreatic cancer, ALS, or deadly childhood diseases? Even if this means that funding devoted to other, more generously-funded diseases must make up the difference?

Part 1 Answer: Research and the NIH priority setting process are inherently dynamic; developing and adjusting to new opportunities and to evolving public health needs. For research priority setting, a major factor in measuring burden is to identify trends and not just to rank different conditions by their current burden. NIH asks questions including: Is there an emerging problem? Will it grow in the future? Has there been any progress in preventing a disease or managing a condition? For some diseases, measures of

incidence or prevalence are relatively accessible. For other diseases and conditions, measures, such as death rates or hospitalizations, provide more accessible indicators of trends in disease burden.

NIH priority setting including the level of funding associated with a specific disease or condition reflects the collective advice and judgment of several different stakeholders with regard to the promise of various research opportunities and the best way to capitalize on those opportunities to reduce public health burden. These include:

- the individual investigators and teams of investigators as they identify research topics which they consider to be significant problems and develop proposals;
- scientists who serve on peer review study groups to review and score proposals based on their professional assessments;
- Institute and Center (IC) program officers who rely on their own expertise and seek consultation from the scientific community as they identify gaps and opportunities in a particular disease area or field of investigation. Addressing these gaps and opportunities may become program priorities and fostered via Funding Opportunity Announcements;
- IC advisory groups made up of members from the public and from the medical and scientific communities who provide a secondary review of research proposals and provide advice to IC directors regarding funding of individual projects and balancing the overall IC portfolio across multiple disease areas and fields of investigation;
- advisory groups of outside experts to assess trans-NIH activities (*e.g.*, the reviews of the NIH intramural research program and AIDS research program) and to recommend budgetary and programmatic improvements;
- patient organizations and voluntary health associations; and
- Members of Congress, who provide legislative direction; and other Federal agencies who provide consultations, opinions, and advice for both budgetary and programmatic insight, *e.g.*, the Centers for Disease Control and Prevention (CDC) and the Department of Defense (DoD).

The relationship between scientific opportunities, burden of illness, and disease-specific funding is multifaceted and not always straightforward or linear. The distribution of funding for any year is but a snapshot of an evolving process.

The amount of NIH funding identified with a particular disease is not a complete picture of the attention paid to that condition. It fails to reflect the likely benefits of basic research or findings from research coded to other conditions. In many situations, progress on a specific disease may be limited by a lack of basic biologic insight about the condition. In that situation the best approach for alleviating burden for a particular condition will be to fund more basic, non-disease-specific research to address knowledge gaps. While aimed at advancing disease-based research for one or more conditions, such projects may be classified as basic research for recordkeeping purposes and are not necessarily catalogued as funding for any specific disease or conditions. Also, new scientific opportunities often flow from NIH-sponsored research on broad scientific themes (such as genome projects, development of instrumentation, training in clinical research, or developments in basic science). Historically, support of these themes has often yielded insights and capacity to stimulate research to address one or more specific diseases. An exclusive focus on a few key diseases would be inherently inequitable and would eliminate hope for millions of individuals who suffer from a range of painful or debilitating chronic conditions, including so-called rare or orphan diseases.

Question 3, Part 2. For example, pancreatic cancer remains one of the top 5 sources of cancer death in the US, but receives considerably less funding than the others in that category.

Answer: Public health burden, including factors such as disease incidence and mortality, is always a consideration for allocating NCI funding. It is one of many factors considered when allocating funds from the NIH and NCI budgets; other factors include scientific opportunities and the quality of the research proposals we receive. Determining public health needs requires a complex evaluation of many aspects of disease, taking into consideration trends, not just data from a single year.

NIH and NCI set priorities based on both burden of illness and our collective assessment of how best to reduce the burden associated with specific diseases; these include the identification of topics on which our knowledge is deficient, as well as a determination of how best to capitalize on scientific opportunities for making progress.

It is customary for NCI leaders, investigators in our research communities, and scientific program managers to periodically review progress towards critical goals and to “scan the horizon” for methods and ideas that could be employed to nurture future efforts. The NCI is using its established Clinical and Translational Advisory Committee to oversee such reviews and “horizon scans” for several cancers, including pancreatic cancer, that have proven refractory to improvements in prevention, early detection, and treatment. The subcommittees being formed to conduct these surveys will include subject experts, Cancer Center directors, and other well-established investigators in cancer research. The intent of these exercises will be to determine whether the NCI has been employing the full range of its talents and methodologies to study such cancers; whether significant progress has occurred; and how the institute can be more effective in the future in pursuit of the goal of reducing the morbidity and mortality of every type of cancer.

Question 4: Though I’m not a scientist, I’ve long believed that we must consider our modern environment when it comes to the source and progression of certain diseases. Environmental factors can include chemical and radiation exposure, diet, medicines, pollutants, and the rest. It seems to me that finding links between these factors and disease – and then addressing them – could be easier and more cost-effective than creating new personalized molecular or biologic treatments to cure disease. Do you share this view? Can you speak to the role of environmental health science research under your leadership at NIH?

Answer: NIH is committed to preventing and treating disease,. Promoting a healthy environment is an important way we can improve our health, and our efforts to understand the role of environmental exposures in disease have NIH’s strong support. NIH’s environmental health institute, the National Institute of Environmental Health Sciences (NIEHS), is committed to pursuing the research to help achieve this goal. The vision for the NIEHS articulated in the Institute’s new Strategic Plan is “to provide global leadership for innovative research that improves public health by preventing disease and disability from our environment.” NIEHS scientists and grantees conduct research on environmental influences on a wide range of diseases, including , asthma, , reproductive dysfunctions, obesity, liver disease, and birth defects, among many others. Our nation’s health status will benefit enormously if we are able to prevent disease through improved understanding of potential environmental contributions and reduction in exposure. Moreover, NIEHS’s research isn’t conducted in a vacuum; the same advances in our knowledge of genetics and molecular biology of human systems that drive therapeutic drug development are being used by NIEHS investigators to understand the molecular basis of individual susceptibility to environmental agents. Ultimately, our efforts to understand and prevent human disease will depend on how well we understand not just our own biology, but all the ways in which our biology and our genes interact with our environment. Part of this effort includes the National Children’s Study (NCS), led by NIH with the collaboration of a consortium of Federal agency partners including the CDC and the Environmental Protection Agency. The NCS, which was mandated by the Children’s Health Act of 2000, is a longitudinal birth cohort study that includes pregnant women and some women preconception to investigate the role of environmental influences (such as air, water, diet, family dynamics, community and

cultural influences, in combination with genetics) on children's health and development. A core focus of the NCS is the establishment of a data, biospecimen, and environmental sampling resource to help answer important questions, including ones about the potential effects of prenatal exposures to environmental agents, that will provide information scientists may be able to use to help prevent diseases and disabilities from occurring in children.

Question 5. I'm curious about what concrete scientific progress or research goals were met with the \$10.4 billion in stimulus funds allocated to NIH. Some of the grants that have apparently been funded include the following:

- How does falling in love and breaking up affect stress? (\$401,955)
- What stigmas do people associate with marijuana, and does this affect their use? (\$226,321),
- Same for alcohol, (\$406,758)
- "Hook-up" habits for girls who are freshmen in college: Doesn't drinking lower their inhibitions? (\$398,948)
- Does porn help people quit smoking? What about images of mutilation? (\$434,487)
- Do hand held video games calm kids down in the ER? (\$522,955)
- Do drugs lead to risky sex choices? (\$417,645)

Dr. Collins, Congress shouldn't dictate science to the NIH, but do you think this is how Americans with serious diseases wanted NIH stimulus dollars spent?

Answer: NIH's goal for the \$10.4 billion allocated to it in the American Recovery and Reinvestment Act (ARRA) was to award the funds to proposals making significant contributions towards advancing science and improving the scientific infrastructure across biomedical and behavioral disciplines, with the ultimate goal of improving public health. The influx of ARRA funding allowed the biomedical research community to speed up discovery by hiring new staff, purchasing new equipment, and in many cases providing the sole funding for new projects that otherwise would have been postponed or not funded.

Several studies applied ARRA funds to investigate a range of genetic disorders and diseases using new gene scanning technology. For example, ARRA funding was crucial to the expansion of the Cancer Genome Atlas (TCGA) - a large-scale collaborative effort and resource with the goal to characterize all relevant genomic alterations in a variety of human cancers. The aim of this effort, and others like it, is to ultimately lead to personalized cancer treatment that is precisely matched to the patient's particular tumor type. With ARRA funding, TCGA expanded to include additional cancer types and tumor samples from 2 to more than 20 tissue types; 10 times the number of tumor types than would have been possible without ARRA funding.

In addition, ARRA funding was used to support the largest study ever conducted into possible genome-associated factors of Alzheimer's disease. By examining DNA samples from more than 56,000 study participants, investigators were able to confirm one gene variant and identify several others as risk factors for developing late-onset Alzheimer's. Identifying measurable risk indicators could make it possible to initiate prevention and treatment interventions far earlier in the course of the disease.

ARRA funding has also helped improve the screening, diagnosis, and treatment of Autism Spectrum Disorder (ASD). Using brain imaging technology, called diffusion tensor imaging (DTI), researchers were able to measure differences in tracts of neuronal fibers that conduct long-distance communications between brain regions. This non-invasive, anatomically-based imaging technique also allowed investigators to distinguish individuals with ASD with high accuracy, providing insight not only into the neurological underpinnings of these disorders, but also providing a potentially powerful screening tool.

In another ARRA-funded project, researchers developed and tested a class of small molecules which can modulate the activity of hormones - oxytocin and vasopressin, which can affect the stress response - with therapeutic potential to ameliorate symptoms of anxiety and stress in ASD patients. As a result of Recovery Act funding, a number of discoveries have been made that will benefit many serious diseases, including autism.

In regards to the specific grants you inquired about, all of which involve behavioral research, it is important to note that human behavior accounts for almost 40 percent of the risk associated with preventable premature deaths in the United States. Health-injuring behaviors, such as smoking, excessive alcohol consumption, and drug abuse, as well as inactivity and poor diet, are known to contribute to many of the diseases and adverse health conditions that NIH is trying to prevent and reduce. Research grants that may have intriguing titles, nonetheless have meritorious scientific goals aimed at informing effective interventions. For example, high-risk sexual behavior takes an enormous public health and economic toll on society in sexually transmitted diseases and unplanned pregnancies. The research you cited on the sexual behavior of female college freshmen will inform the development of educational, medical, and public health interventions to prevent high-risk behaviors in young women. As another example, increased sexual risk behavior is a major avenue by which drug dependence contributes to the risk of contracting HIV/AIDS. Preventing HIV infection is NIH's highest priority for HIV-related research. Therefore, it is important to study the basic decision-making processes related to sexual HIV risk behavior to determine which decision-making processes are most relevant to target in HIV prevention efforts.

The NIH website¹² has more information about the impact of NIH ARRA funding on research and the economy, and we will continue to update the site on an ongoing basis to provide a comprehensive picture of NIH's ARRA activities and results.

¹² <http://recovery.nih.gov/>.

The Honorable Tim Murphy**Question 1: What is the NIH willing to do to place a greater priority on research into primary mitochondrial diseases?**

Answer: Mitochondrial diseases are progressive and crippling disorders. NIH is working with the North American Mitochondrial Disease Consortium (NAMDC) and the United Mitochondrial Diseases Foundation (UMDF) to address these challenges. NAMDC, a part of the Rare Diseases Clinical Research Network (RDCRN), is funded by the National Institute of Neurological Disorders and Stroke and the Eunice Kennedy Shriver National Institute of Child Health & Human Development. The Office of Rare Diseases Research, part of the National Center for Advancing Translational Sciences, provides oversight of the RDCRN and funds several consortia within the RDCRN as well as the Data Management and Coordination Center which is a resource for all RDCRN consortia, including the NAMDC. The NAMDC has begun work on an integrated, international patient registry for 28 mitochondrial diseases at 10 clinical centers across the United States and Canada in collaboration with the UMDF. The consortium conducts integrated, multi-project, and multi-institution research in primary mitochondrial diseases, while also training the next generation of primary mitochondrial diseases researchers.

Implementing recommendations of a recent scientific conference, NIH formed a trans-community working group on primary mitochondrial diseases. Members include representatives of all segments of the mitochondrial disease communities, the NIH Institutes, Centers, and Offices, and other agencies of the Federal Government, the UMDF and relevant patient advocacy groups, scientists, and patient representatives. A sub-group consists of NIH representatives who will translate the ideas of the larger group into research initiatives that focus on primary mitochondrial diseases. An analysis of the NIH research portfolio by the trans-community working group is expected to contribute to an overall increase of research portfolio efficiency and elimination of any possible research redundancy. Although Common Fund programs do not focus specifically on mitochondrial diseases, the Common Fund issued 20 awards in FY 2011 that are relevant to these conditions. Most of the awards were funded as part of the High Risk/High Reward Program¹³ which includes the Pioneer, New Innovator, Transformative Research Awards, and Early Independence Award initiatives.

Question 2: How can the NIH further promote collaboration and coordination on primary mitochondrial disease research among the Institutes and with other organizations?

Answer: NIH is promoting collaborations in a number of ways. NIH, in collaboration with the UMDF and extramural investigators, organized a scientific conference with members of the mitochondrial disease research and patient communities. Extramural researchers, NIH program representatives, intramural scientists, and patient advocates met on May 8-9, 2012, to discuss barriers to and opportunities in primary mitochondrial diseases research. One of the results of this conference was the realization of the need for better communication and coordination. A trans-community working group was formed involving all segments of the primary mitochondrial diseases community. A sub-group of NIH representatives will implement the recommendations of the larger group into research initiatives that focus exclusively on primary mitochondrial diseases.

¹³ See <http://commonfund.nih.gov/highrisk/>.

The Honorable Michael Burgess

Question 1: I read with concern in the Information Technology and Innovation Foundation and United for Medical Research report that the U.S. role in leading biomedical science is under threat; that other nations want to take that title from us. Is that true? What is the long-term implication of slipping to second, third or lower?

Answer: The United States is by far the largest R&D performer globally, contributing \$402 billion in 2009 and accounting for about 31 percent of the global total. However, the Information Technology and Innovation Foundation and the advocacy group United for Medical Research suggest in their report, *Leadership in Decline: Assessing U.S. International Competitiveness in Biomedical Research*, that the United States' leading edge in science may be declining. Public investments in the life sciences translate into jobs, other economic gains, and a healthy society. They spur the private sector, generating beneficial catalytic reactions throughout the economy. Moreover, many have suggested that the life sciences have the greatest potential among all areas of science for dynamism and growth in this century. Innovation and discovery in the life sciences are, thus, crucial to a vibrant economy and, thereby, to a strong, secure, and flourishing America. The United States Government continues to remain committed to supporting biomedical research, as the recent influx of funding through the American Recovery and Reinvestment Act demonstrated. It allowed the biomedical research community to speed up discovery through the hiring of new scientists and to purchase new equipment, and, in many cases, it provided the sole funding for new projects (including construction projects) that otherwise would have been postponed.

Question 2. Dr Collins – you were the head of the Genome project – Are we seeing the results of genomic medicine? Has the sequencing of the genome paid off?

Answer: Yes, we are clearly seeing the investment in the Human Genome Project (HGP) pay off as we increasingly leverage the knowledge gained to understand human biology. At this point, much of the return is seen through research advances that expose the biological underpinnings of disease and disease progression, which in turn informs translational research and the early clinical applications of genomic medicine. That said, genomic medicine already is having an effect within certain medical specialties, notably in oncology where diagnostics for genetic and genomic markers are increasingly used in cancer screening and to guide treatment strategies. For example, the widespread use of BRCA testing in patients with familial risk factors for breast and ovarian cancer, the use of OncotypeDX to predict disease recurrence, and the use of genetic and genomic diagnostic tests to determine the suitability of particular therapeutic treatments. Findings generated through the work of The Cancer Genome Atlas confirm that cancers that appear morphologically similar (e.g., glioblastoma multiforme) can be separated into distinct genetic subtypes, only some of which respond to current therapies. Determining the mutated genome of a patient's tumor can therefore prevent the use of harsh chemotherapeutic drugs unable to effectively target and treat that tumor type. From less complex diagnostic tests used to predict the effect of trastuzumab (Herceptin®) use in breast cancer, vemurafenib (Zelboraf®) use in melanoma, or crizotinib (Xalkori®) in lung cancer, to more advanced strategies of sequencing the mutated genome within a patient's tumor and comparing it to the genomic information in their unaffected cells as a means to guide treatment, genomically informed medicine is becoming a powerful tool to inform clinical care.

Beyond cancer, genomics is fueling major strides in other clinical areas as well. NIH's intramural Undiagnosed Diseases Program applies genomic analyses to cases that have stumped the medical community. To date, two new diseases have been discovered and fifty patients have received long-sought diagnoses. Similar approaches using whole genome sequencing to diagnose a rare disease have been used in recent high profile cases in Wisconsin (Nic Volker) and California (Noah and Alexis Beery). Beyond applications for disease identification or categorization, a promising study at Stanford University showed that DNA sequencing can be used to non-invasively monitor organ transplant recipients to detect early

signs of tissue rejection. Another study, also conducted at Stanford University, used genomics to screen a library of existing FDA-approved drugs to determine whether they might be repurposed for use in other diseases. Through this work, the possibility of repurposing an epilepsy drug for use in ulcerative colitis and Crohn's disease, and using an anti-ulcer drug to treat certain forms of lung cancer has been highlighted.

It is worth noting that although the primary aim of the HGP was to improve health, the project's effects have not, and will not, be confined to the clinic. A report published last year by Battelle Technology Partnership Practice, *Economic Impact of the Human Genome Project*, showed that the HGP has had a significant positive impact on the United States economy. The report estimates that between 1988 and 2010, Federal investment in genomic research generated an economic impact of \$796 billion, an impressive effect considering that HGP spending between 1990-2003 amounted to \$3.8 billion. The Battelle Report further found that in 2010, the genomic sector directly supported more than 51,000 jobs, indirectly supported more than 310,000 jobs, created \$20 billion in personal income, added \$67 billion to the United States economy, generated more than \$3.7 billion in Federal taxes, and generated more than \$2.3 billion in State and local taxes.

Question 3. Today, 5.3 million Americans are living with Alzheimer's disease, and nearly 16 million people will have the disease by the middle of the century.

In May, the NIH convened an Alzheimer's disease research summit. According to the recently released National Alzheimer's Plan, it is expected that NIH will release a report summarizing the Alzheimer's research summit in August. What should we expect to see in the report?

- i. **How will this information be used to set forth changes in the prioritizing and funding of Alzheimer's research across the NIH? Are there larger policy ideas that will be discussed that might need the attention of this Committee?**
- ii. **It's my understanding that we are at a scientific tipping point – there are huge scientific opportunities that are waiting to be undertaken in order to save millions of lives and result in significant returns on our investment. What in the view of NIH are the three to five scientific topics related to Alzheimer's most in need or ripe for a targeted investment from NIH and other funders, including the private sector?**

Answer: An initial list of recommendations from the NIH Alzheimer's Disease Research Summit, held May 14-15, 2012, is available on the National Institute on Aging (NIA)'s website,¹⁴ and a final transcript of the meeting is expected in the fall. NIH will use the recommendations to identify research priorities and milestones for measuring progress toward the goal of accelerating delivery of successful treatments for Alzheimer's Disease (AD). The recommendations focus on a spectrum of basic discovery and translational research activities critical to the development of disease-modifying, as well as symptomatic therapies across the disease continuum for the cognitive and neuropsychiatric symptoms of Alzheimer's disease. They also identify the types of infrastructures, resources, and new public private partnerships needed to successfully implement this translational agenda.

Although the Summit recommendations most relevant to the NIH mission involve the support and pursuit of cutting-edge science, some broader scale policy issues discussed in the recommendations may eventually come to the attention of this Committee. For example, Summit participants pointed to intellectual property barriers to drug development and the need for new strategies to overcome these barriers in several of the Summit sessions. In addition, it will be important to leverage public and private

¹⁴ <https://auth.nia.nih.gov/newsroom/alzheimers-disease-research-summit-2012-recommendations>.

collaborations in order to implement and translate research discoveries into treatments and clinical practice.

Recent years have seen an acceleration of discovery with promising new opportunities for progress toward identifying effective prevention and treatment interventions for AD. The most effective approach to addressing this goal will involve prioritized research at several levels:

- 1) **Basic research to identify potential targets for intervention.** We have gained tremendous new insights into the basic biology underlying AD, but a critical question remains about which target, or targets, will ultimately be most effectively translated to clinical interventions. It is therefore essential that we continue to support basic research to identify and validate molecular and genetic pathways as targets for intervention.
- 2) **Translational research to identify the *best* targets and develop effective treatment strategies.** Once we have identified potential targets for intervention, we must next identify ways in which those targets can be attacked to prevent, slow progression of, or reverse damage or loss of nerve cells in brains affected by AD.
- 3) **Clinical trials to test the most promising interventions.** Several advances have created the opportunity to design trials of treatment or prevention that were not previously possible. The discovery of brain imaging changes and other biomarkers now allows us to identify early stages of the AD process many years before any symptoms have developed, and hopefully before irreversible damage has been done to the brain. This will allow us to test prevention strategies in individuals with a high risk of developing AD, years or decades before they develop symptoms; in addition, it will enable us to follow the trajectory of imaging and other biomarkers to determine if the experimental intervention is effective.

These three major avenues of high priority research will provide an effective pathway from discovery of new targets to their rapid translational pre-clinical screening, and to ultimate identification and clinical trials of the most promising treatments and prevention strategies.

Question 4. With regard to the proposed merger of the Institute on Substance Use and Addiction Disorders with the National Institute on Alcohol Abuse, there have been concerns about procedure and transparency along the way. A few examples: there doesn't appear to be a mission statement yet. Also, I've not seen a cost analysis of the administrative and logistical functions of combining two institutes. I'm also curious what the impact would be on the employees of these two institutes. Have you addressed these questions, and what is your plan for stakeholder involvement moving forward, in terms of creating a definition for addiction and how to allocate the research at the existing institutes, and those sorts of things?

Answer: We will work with the Committee to address your concerns.

Question 5. Director Collins, do you believe that the existence of multiple national and international patient registries has accelerated and assisted in the development of new treatments and therapies for cancer that have been widely successful?

Answer: Yes. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is a coordinated system of population-based cancer registries strategically located across the United States. Cancer registries such as SEER monitor cancer trends and provide timely, accurate, and continuous data on cancer incidence, the extent of disease at diagnosis, therapy, and patient survival. While cancer registries are not directly used for the development of new treatments and

therapies, the registry activities do support the development and delivery of these new treatments and therapies for cancer.

National and international cancer registries have accelerated and assisted in the development of new treatments and therapies for cancer that have been widely successful. Almost any study of new treatments and therapies takes advantage of cancer registries, from those that focus only on patients in one hospital to those that are developed and maintained by non-governmental organizations to population-based registries that capture all of the cancer cases in large geographical areas. These registries are used by researchers for many purposes including determining whether a specific form of cancer among the many biological types of cancer occur in excess in some particular place, what segments of the population are most at risk and the characteristics of people who develop the cancer; identifying which hospitals or geographical areas have large enough numbers of patients with the appropriate demographic and clinical characteristics to include in research studies; and reporting survival for patients with specific types of cancer. Cancer registry data are also used to estimate the prevalence of rare cancer for inclusion in FDA's orphan drug designation programs that provide incentives for the development of products for rare diseases. Additionally, rapid case ascertainment enables researchers to identify patients eligible for enrollment in clinical trials.

As scientists and researchers come to better understand cancer as a constellation of diseases, monitoring and measuring the prevalence of cancers is important to identify new therapeutic targets for treatment development. An example of this is the role played by the SEER Utah Registry, through its inclusion in the Utah Population Database (UPDB), in the discovery of the link between increased risk of breast and ovarian cancer and mutations in the BRCA1 and BRCA 2 genes.¹⁵

Cancer registries also play an important role in measuring the implementation of, and having an impact on, new treatments and therapies in clinical practice. For example, the NCI Patterns of Care/Quality of Care (POC) studies rely on SEER registry data to provide important information on cancer treatments, evaluate the diffusion of state-of-the-art cancer therapy into community practice, disseminate findings from these studies to the scientific community, and work with professional organizations to improve quality care in community practice. POC studies provide findings that may inform strategies to decrease disparities in treatment and survival among different population groups.

Finally, as cancer registries increase their use of electronic sources in the collection of data, they will be in a position to better assist in developing new treatments and monitor the implementation of these therapies in clinical practice.

Question 6. Given your expertise and NIH's substantial experience and resounding success in creating and operating patient registries for many diseases, including many designed to assist in the battle against many cancers, including breast cancer, would you not agree that a national registry for PF would be likely to accelerate existing research and help attract new research that is not happening because of the absence of such a basic research tool?

Answer: The National Heart Lung and Blood Institute (NHLBI) is engaged in ongoing discussions with academic researchers, scientific/medical societies, and patient advocacy groups about capitalizing on research opportunities in pulmonary fibrosis (PF). The Institute continues to provide research infrastructure for PF as an integral part of the Lung Tissue Research Consortium (LTRC) and to support the NHLBI Idiopathic Pulmonary Fibrosis Network (IPFnet).

¹⁵ <http://hitexchangemedia.com/articles/julyaugust-2011/inside-the-utah-population-database/>.

A national registry for PF could be an important tool for advancing PF research by providing information on PF natural history and epidemiology, as well as providing a platform for facilitating recruitment for clinical studies. The LTRC and IPFnet represent excellent opportunities for leveraging such a registry. In March 2012, NHLBI met with other stakeholders to discuss establishing a PF registry and bio-repository. The broad consensus from that meeting is that NHLBI will continue its support for a PF bio-repository as an integral part of LTRC while the academic researchers and a patient advocacy group (Pulmonary Fibrosis Foundation) will move forward with establishing a PF patient registry. In June 2012, NHLBI had a follow-up discussion with the Pulmonary Fibrosis Foundation regarding their plans for pursuing a PF registry, which include using some centers from the NHLBI-sponsored IPF Clinical Research Network because of their strong expertise in recruiting PF patients and accurately diagnosing the disease.

Question 7. Although the NIH has been asked repeatedly by the House & Senate Appropriations Committees and many Members of Congress to develop and implement a long-term and comprehensive strategic plan to approach pancreatic cancer research, they have failed to do so.

- i. **Many Members of Congress are hesitant to earmark funding at NIH for specific diseases, and with good reason. We should leave those decisions to the experts. For 10 years, Congress has asked NCI to produce a strategic plan to address a mid to long term strategy in dealing with pancreatic cancer. NCI has not responded to these requests, or has responded weakly. The fact is, NCI and NIH still lack a long term strategy in dealing with pancreatic cancer. Dr. Collins, what is the plan? Do you have one? If not, why not, as Congress has been requesting you develop a strategy for a decade now.**

Answer: The NCI's Investment in Pancreatic Cancer Research (FY 2011)¹⁶ includes progress reports on NCI's implementation of recommendations from the 2001 Pancreatic Cancer Progress Review Group.

Additionally, in 2008, the NCI Gastrointestinal Steering Committee convened a "Clinical Trials Planning Meeting on Pancreas Cancer Treatment," to discuss the integration of basic and clinical knowledge in the design of clinical trials in pancreatic ductal adenocarcinoma (PDAC). A Consensus Report from this meeting was published in the *Journal of Clinical Oncology* in November 2009.¹⁷ The committee placed major emphasis on three areas: enhancement of research to identify and validate the relevant targets and molecular pathways in PDAC, cancer stem cells, and the microenvironment. The committee also identified additional research priorities, including development of combination therapies and predictive biomarkers. The Consensus Report has helped to guide many of the NCI's pancreatic cancer research efforts over the past three years.

Nevertheless, it is important to observe that, while we can plan ways to study pancreatic cancer with many methods at our disposal, our understanding of the disease is not yet mature enough to develop a plan for prevention, early diagnosis, and treatment. Consistent with NIH's experience, for advances on important clinical aspects of the disease, it is important to encourage investigators to propose imaginative and technically sophisticated approaches and to fund those that are judged to have strong scientific merit. It is customary for NCI leaders, investigators in our research communities, and scientific program managers to periodically review progress towards critical goals and to "scan the horizon" for methods and ideas that could be employed to nurture future efforts. The NCI is using its established Clinical and Translational Advisory Committee to oversee such reviews and "horizon scans" for several cancers, including pancreatic cancer, that have proven refractory to improvements in prevention, early detection, and treatment. The subcommittees being formed to conduct these surveys will include subject experts, Cancer Center directors, and other well-established investigators in cancer research. The intent of these

¹⁶ <http://www.cancer.gov/researchandfunding/reports/pancreatic-action-plan.pdf>.

¹⁷ <http://jco.ascopubs.org/content/27/33/5660.full.pdf>.

exercises will be to determine whether the NCI has been employing the full range of its talents and methodologies to study such cancers, whether significant progress has occurred, and how the Institute can be more effective in the future in pursuit of the goal of reducing the morbidity and mortality of every type of cancer.

- ii. **With respect to pancreatic cancer, we have made some strides toward understanding the basic biology of the disease in the last decade, such as understanding some of the complexities of the disease. For example, we now understand that pancreatic cancer tumors differ from most other tumor types, making it one of the most challenging cancers to research. But the translation of these findings to patient benefit is still long-term and underscores the need for a focused effort in pancreatic cancer. What are your specific plans for translating these discoveries into clinical care and improving the dismal survival rates for pancreatic cancer?**

Answer: The NCI continues to support a diverse pancreatic cancer research portfolio, including research focused on the translation of basic findings to clinical applications. Examples of specific NCI-supported initiatives already underway include research in the following areas:

- **Preclinical Models:** Recent research, building upon NCI investments in preclinical models of pancreatic cancer, indicates that instillation of an enzyme called PEGPH20 can also increase delivery of the chemotherapy gemcitabine to mouse pancreatic tumors. This approach resulted in a significant increase in survival time. An early-phase clinical trial, led by an investigator at the Fred Hutchinson Cancer Research Center, an NCI-designated Center, is underway to test the combination in people with metastatic pancreatic cancer.
- **Clinical Trials:** NCI is currently supporting 62 active pancreatic cancer clinical trials, including a 950-patient trial – the largest of its kind – to evaluate the benefit of adding a targeted drug and/or radiation therapy to combination chemotherapy. NCI is also supporting immunotherapy research for advanced pancreatic cancer, including a trial of the targeted drug ipilimumab, and another studying the effect of the administration of tumor-infiltrating lymphocytes – isolating these white blood cells from surgically removed pancreatic cancer metastases, and mobilizing the cells to work against the tumor.
- **Targeted Therapies:** In 2012, NCI-supported researchers demonstrated that inhibition of an enzyme known as protein kinase C delta (PKCD) is toxic to pancreatic cancer cells. Since the PKCD enzyme is tumor-promoting in the presence of mutant K-RAS, it is possible that a small molecule inhibitor of PKCD could have potential as a targeted therapy for pancreatic tumors, and other cancers with K-RAS mutations. While this particular study focused on pancreatic cancer cells, the authors, based at the Boston University Cancer Center, conduct research exploring the basic molecular and cellular biology of various cancer types. NCI-supported research will continue to build upon these findings in an effort to determine whether PKCD inhibitors have clinical applications for pancreatic and other cancers.
- **Combination Therapy:** NCI-supported research also includes analysis of the recent findings that losartan, a drug commonly used to treat hypertension, has been shown to “open” compressed tumor vessels and make dense pancreatic cancer cells more permeable to anti-cancer drugs. Efforts are underway to test whether adding losartan to standard therapy can improve survival.

The Honorable Marsha Blackburn

Question 1: Many universities in Tennessee will soon be beginning their next fiscal year, and as such have already begun planning cutback based on the sequester that is scheduled to begin January 2, 2013. Can you tell us what kind of planning is being done at NIH to deal with the potential sequester? What advice do you have for NIH grant recipients as they look to plan for the year ahead?

Answer: NIH would continue to prioritize support for the most promising biomedical research proposals and endeavor, to every extent possible, to minimize disruption to the scientific workforce. Reductions in basic research funding could slow the discovery of fundamental knowledge about human health and disease. Research supporting the prevention of debilitating chronic conditions that are also costly to society could be deferred or curtailed. A wide array of clinical trials for more precise tests and more effective treatments of common and rare diseases affecting millions of Americans could be scaled back, delayed, or halted. Some projects could be difficult to pursue at reduced levels and some could be cancelled, putting prior year investments at risk.

As the Administration has made clear, no amount of planning can mitigate the effect of these cuts. Sequestration is a blunt and indiscriminate instrument and the President has stated it is an irresponsible way for our Nation to achieve deficit reduction. The Administration stands ready to work with Congress to get the job done.

Question 2: I am sure that everyone recalls the doubling of the NIH budget that took place during the last decade. I think we also know that these are very difficult times for funding, given our current economic problems. Having said that, a recent report from United for Medical Research (UMR) entitled “Leadership in Decline: Assessing U.S. International Competitiveness in Biomedical Research” suggests that U.S. leadership in biomedicine is under serious threat, and that other countries, including China, will soon overtake us in this area. Do you agree with that assessment? What steps can and should the Federal Government take to ensure continued American leadership in biomedical research?

Answer: The report by the Information Technology and Innovation Foundation and the advocacy group United for Medical Research, *Leadership in Decline: Assessing U.S. International Competitiveness in Biomedical Research*, assesses the global “state of play” in biomedical research and the life sciences in general. It suggests that the United States’ leading edge in science may be declining. Between 1999 and 2009, Asia’s share (including China, India, Japan, Malaysia, Singapore, South Korea, Taiwan, and Thailand) of worldwide R&D expenditures increased from 24 percent to 32 percent, with China at 12 percent and Japan at 11 percent. Also, the European Commission recently urged its member nations to increase their investment in research by a substantial margin, recommending budgets of €80 billion (\$108 billion) in 2014–2020, a 40 percent increase over the previous seven year period. Despite these concerns, the United States remains by far the largest R&D performer globally, contributing \$402 billion in 2009 and accounting for about 31 percent of the global total,

In order to maintain United States leadership in biomedical research, the Federal Government will continue to seek innovative solutions to ensure rapid advances in science. This will require stable and strategic investments in research with the highest potential for improving public health, and flexibility to move quickly to capitalize on unexpected scientific opportunities or respond to new public health threats. Another key to maintaining United States leadership is ensuring a robust biomedical workforce now and in the future by investing in education at all levels.

Question 3. Two relatively new areas at NIH are the National Center for Advancing Translational Sciences (NCATS) and the Cures Acceleration Network (CAN). NCATS is the home of the Clinical and Translational Science Awards (CTSAs) and Vanderbilt University in my state is the coordinating center for all of the 60 institutions linked by the CTSA program. Thanks to the CTSA program and other NIH funding, Vanderbilt is already working on treatments for Parkinson's, Alzheimer's and even schizophrenia. Can you tell us how you expect NCATS and CAN to interact, and what you expect to see in terms of outcomes?

Answer: The newly established NCATS is home to both the CTSAs and CAN, and the missions of these two programs are highly complementary. The CTSAs are major awards to 60 medical research institutions across the nation to provide support and infrastructure for the entire spectrum of translational research. These institutions have established extensive research infrastructure to support the effective translation of research discovery into improved patient care. CAN is intended to fund initiatives to address scientific and technical challenges that impede translational research, and to advance the development of "high need cures" by accelerating the pace and reducing the time between research discovery and therapeutic treatment.

Both CTSAs and CAN are critical to support the NCATS' mission to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

NCATS has launched the Tissue Chips for Drug Screening initiative, funded through CAN, to design bioengineered tissue chips that researchers can use to predict the performance of a candidate drug, vaccine, or biologic agent quickly and inexpensively. Several of the applications for this award have been submitted by institutions that currently have CTSAs. Should any of these be funded, there will be an opportunity to leverage CTSA investments to help advance this effort.

Also to be funded through CAN is the recently announced Discovering New Therapeutic Uses for Existing Molecules initiative, where NCATS is partnering with eight leading international pharmaceutical companies that have provided 58 compounds/molecules for repurposing. We expect applications from CTSA institutions.

NCATS has actively solicited input in the best strategies to utilize CAN's new flexibilities to advance the development of "high need cures" and reduce significant barriers between research discovery and clinical trials. In June 2012, the IOM held a workshop on maximizing the goals of CAN to accelerate the development of new drugs and diagnostics. The summary will be available later this year and should provide further guidance to NCATS in supporting CAN and its interaction with CTSAs.

Question 4 and 5. Publishers of scientific and medical journals have expressed concerns with the implementation of the NIH public access policy and that NIH is reluctant to collaborate with them and instead seems more intent on competing with them.

What are the potential impacts of PubMed Central on publishers, and how do you assess/measure/track these? How are you working collaboratively with publishers? What steps have you taken to alleviate concerns that NIH is focused on competing with publishers rather than collaborating?

Combined Answer: NIH does not compete with publishers; rather it collaborates with them in a number of ways to improve access to the results of scientific research. Notably, NIH funds the research that is

reported in scientific journal articles, as well as the preparation of manuscripts that are submitted freely to publishers for publication. NIH also permits funded scientists to use their NIH awards to cover some or all of the costs of publishing, such as page charges and open access fees. In total, NIH funding results in more than 90,000 peer-reviewed scientific papers per year.

The NIH Public Access Policy ensures that the public has access to the published results of NIH-funded research by making these papers available without charge on PubMed Central (PMC). It puts quality research in the hands of scientists in industry and academia to accelerate the pace of discovery. It also helps create a central repository of biomedical information, PMC, which serves multiple audiences from researchers to students, and from doctors to entrepreneurs.

The NIH Public Access Policy has been designed to minimize impact on publishers. It makes articles publicly available via PMC as long as 12 months after the official date of publication. NIH originally proposed a 6-month embargo that was later changed to 12-months in response to concerns raised by publishers, although scientists would prefer immediate access to articles in PMC. Numerous other research funding organizations now have public access policies with embargo periods of six months or less. Further, the NIH Public Access Policy requires only the author's final manuscript to be made public, not the final published version. In addition, every paper posted to PMC includes a link to the paper on the publisher website, which drives hundreds of thousands of clicks to publisher websites every day.

NIH has been collaborating with publishers on the public access policy for a number of years.

- Publishers of almost 1,100 journals voluntarily submit the full content of their journals to PMC, regardless of whether the issue contains an article subject to the NIH Public Access Policy.
- Several hundred journal publishers voluntarily deposit final published versions of NIH-funded articles in PMC automatically on behalf of their authors.
- Thousands of journals voluntarily submit peer-reviewed author manuscripts to PMC to assist authors in complying with the Public Access process.
- The publishers of two of the most prestigious scientific journals, *Science* and *Nature*, recently reaffirmed publicly their support for the NIH Public Access Policy.

The public access requirement took effect in 2008. While the United States economy suffered a downturn from 2007 to 2011, scientific publishing has continued to grow.

- The number of journals dedicated to publishing biological sciences/agriculture articles and medicine/health articles increased 15 percent and 19 percent, respectively, between 2007 and 2011.
- The average subscription prices of biology journals and health sciences journals increased 26 percent and 23 percent, respectively, between 2007 and 2011.
- Publishers forecast increases to the rate of growth of the medical journal market, from 4.5 percent in 2011 to 6.3 percent in 2014.

Question 6. Dr. Collins, in August 2011 the NIH released the study, "Race, Ethnicity, and NIH Grants," detailing that minorities, but particularly African Americans, receive an alarmingly low number of R01 grants. Given that the Research Center at Minority Institutions (RCMI) are the largest producers of underrepresented minority (URM) health professional and biomedical doctoral students, what is your plan to leverage the RCMI program as an existing NIH resource to address the disturbing issue of lower rates of success for African American faculty to obtain competitive NIH grants, even after adjusting for potential mediating factors?

Answer: On June 13, 2012, the Advisory Committee to the NIH Director (ACD) Working Group on Diversity in the Biomedical Research Workforce released a draft report with recommendations to increase

the diversity of the biomedical research workforce.¹⁸ The Working Group recommends that NIH support infrastructure development in those comparatively under-resourced institutions with a documented track record of producing and supporting URM scientists (Recommendation #8). Currently, NIH is reviewing the report and its recommendations and will provide Dr. Collins with implementation options should he accept any or all of the recommendations. It is anticipated that decisions on implementation will be made in the fall of 2012.

Question 7. Dr. Collins, I would like to ask you about how NIH monitors the various sources of US disease burden to ensure that funded efforts are comprehensive and unbiased in meeting the stated NIH mission to “reduce the burdens of illness and disability.” Take the example of migraine which will afflict almost one in five Americans this year and, according to the World Health Organization data, results in almost as many lost years of healthy life annually in the US as HIV/AIDS. Yet in 2011, NIH funded \$16M in migraine-related research compared to \$3.059B for HIV/AIDS, a 191-fold disparity in funding. This isn’t a matter of simply too few quality grant proposals submitted for migraine, but rather that NIH has historically neglected this problem: only once has NIH ever issued an RFA prioritizing migraine research and no NIH CSR study section exists with a focus on migraine to ensure fair peer review of grant proposals. Another example: cluster headache is widely reputed to be the most severe pain that humans can experience, with an alarming suicide rate. It is also as prevalent as multiple sclerosis. Yet, the NIH has not funded a grant on cluster headache research in more than 25 years. How can the NIH ensure that research funding is prioritized relative to the actual sources of national disease burden, so that diseases like migraine or cluster headache do not fall through the cracks?

Answer: NIH does not use one criteria to set research priorities for the agency, nor for the various institutes. Rather, it takes many factors into account including, but not limited to, the burden of disease, the relevance of the disease to the programs supported, and importantly, the scientific opportunities which are available. We also sometimes find that there are areas ripe for funding that lack interested investigators. In those cases, we will offer incentives for investigators to apply for funding set aside by the institutes in order to stimulate interest in the field. This might be especially true for rare and neglected diseases, or areas where progress has not been made.

The NIH system of investigator-initiated research is designed to engage the wisdom of the scientific community throughout the United States to capitalize on scientific opportunity. When investigator initiated-research yields too few meritorious proposals on a disease that causes a large burden, NIH assesses the reasons for the gap and addresses the problem by convening scientific workshops and meetings and issuing targeted funding opportunities and programs. Because migraine and headache cause so great a public health burden, and too little research is underway, NIH has acted recently to increase migraine and headache research.

In May 2010, NIH held a “NIH Headache Research Planning Meeting” with the goal of identifying scientific gaps and opportunities in the headache research field. The meeting brought together clinicians, NIH staff, leaders from the pharmaceutical industry, and members of the patient advocacy community; and resulted in a report with recommendations for moving the headache research field forward. NIH has responded to a number of the key recommendations from the report including (i) holding a follow-up scientific meeting to advance translational headache research; (ii) partnering with public and private entities such as the American Headache Society and FDA to sponsor research symposia, conduct training sessions in grant writing for headache researchers at major scientific meetings, and develop improved analgesic drug trial design; (iii) launching a major pain education initiative - Centers of Excellence in Pain Education - to train clinicians in pain treatment and management, with one Center targeted

¹⁸ <http://acd.od.nih.gov/dbr.htm>.

specifically for training in headache; and (iv) developing a set of common data elements for standardizing clinical research data from headache studies in partnership with key players in the headache research community.

To encourage proposals on research in migraine, NIH has issued specific Funding Opportunity Announcements (FOAs), including “Migraine: Neural Mechanisms and Risk Factors for Progression” and the recently-renewed “Neurobiology of Migraine.” These FOAs have successfully attracted and supported 15 new research grants over the past 5 years. One of these projects, a whole genome association study to identify genes involved in migraine and their interaction with environmental factors, recently identified 3 susceptibility loci associated with migraine. NIH is also supporting research to develop effective migraine therapies and establish clinical practice guidelines. For example, researchers are currently conducting a pivotal trial of drugs to treat pediatric migraine as well as testing the effectiveness of combined behavioral and pharmacological treatments for migraines in children. Most headache applications are reviewed in the Center for Scientific Review (CSR) and the National Institute of Neurological Disorders and Stroke (NINDS) works with CSR to ensure that headache research applications, whether investigator-initiated or in response to targeted solicitations, are peer reviewed in a fair manner and with the requisite expertise. Others, like the recently funded pediatric migraine trial, were reviewed in an NINDS study section dedicated to clinical trial reviews.

NIH also funds a wide range of research relevant to understanding common mechanisms across pain disorders through multidisciplinary initiatives, such as the NIH Blueprint for Neuroscience Grand Challenge on Pain and targeted FOAs in pain research. Areas of focus include sex differences in the pain experience as well as genetic contributions to individual variability and response to treatment. These studies will likely help further our understanding of, and develop treatments for, conditions such as cluster headaches where these factors are thought to play a role.

Question 8. I understand that NIH is working on a plan to merge the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA) in order to create a new addiction-focused Institute. I also understand that instead of putting the proposed merger through the statutory process detailed in the NIH Reauthorization Act of 2006, NIH has decided to include the changes in the FY14 budget to be presented next January or February. Why would you want to make such a change without following the statutory process detailed in the NIH Reauthorization Act of 2006?

Answer: We will work with the committee to address your concerns.

Question 9. There are no clear examples of successful structural mergers within NIH. Additionally, the law requires an assessment of administrative, logistical, and financial costs of abolishing NIAAA and NIDA in favor of one addiction-focused institute. There has been no formal cost assessment done by the NIH. Can you explain to the Committee why you are advising the Secretary of HHS to submit this plan for Congressional approval without the information we need to evaluate its impact properly?

Answer: We will work with the committee to address your concerns.

The Honorable Brian Bilbray

Question 1. Regenerative medicine has demonstrated it has the potential to transform medical care and treat unmet medical diseases. Several products are already on the market and many more are in late-stage clinical trials. What is missing, however, is a national strategy designed to help ensure that the US stays a leader in this field so that it can reach its full potential. A key component of this strategy is policy and research coordination among the various federal agencies. The NIH funds regenerative medicine through several institutes. Please tell me the NIH activities to:

- i. Coordinate its research policies on regenerative medicine among the various institutes.
- ii. Set research priorities and goals across institutes for regenerative medicine.
- iii. Coordinate research projects on regenerative medicine with FDA, Department of Defense and other federal agencies.
- iv. Work with FDA on regulatory science initiative identified as important to advancing product development and approval of regenerative medicine.
- v. Allow for public input into research prioritization in regenerative medicine.

Answer: The National Institutes of Health (NIH) has a robust portfolio of research in regenerative medicine, which includes tissue engineering and cell-based therapy research, and is engaged in ongoing efforts to coordinate research in this area within NIH and across the Federal Government. The primary entity for coordination across the Federal Government is the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group (IWG). Originally organized under the auspices of the Subcommittee on Biotechnology of the National Science and Technology Council (NSTC), the MATES IWG now works independently of NSTC, and is comprised of many Federal agencies and NIH Institutes. The principal purpose of the MATES IWG is to provide a national platform across which member agencies can interact and exchange information on tissue engineering. The membership and interests of the MATES IWG have expanded as both the number of tissue engineering applications and the need to advance the underpinning science have increased. Membership is open to all Federal agencies and their component organizations that have interests or activities related to tissue engineering science. Current membership includes the NIH, the National Institute of Standards and Technology (NIST), DoD, FDA, the National Science Foundation (NSF), the Departments of Veterans Affairs, and the Office of Science Technology and Policy. The MATES IWG meets on a monthly basis to fulfill the following goals: (1) facilitate communication across departments/agencies by regular information exchanges and a common website; (2) enhance cooperation through co-sponsorship of scientific meetings and workshops; (3) monitor technology by undertaking cooperative assessments of the status of the field; (4) provide support for tissue engineering research through interagency funding opportunity announcements; (5) foster technology transfer and translation of research advances into practical applications; and (6) promote the formulation and use of standards for both research tools and product development.

Importantly, the MATES IWG developed a Federal Strategic Plan in 2007 called "Advancing Tissue Science and Engineering: A Foundation for the Future."¹⁹ Examples of recent activities to meet the goals of the strategic plan include the International Assessment of R&D in Stem Cell Engineering²⁰ and the Functional Imaging for Regenerative Medicine Workshop.²¹ I invite you to visit the MATES website where you can find a wealth of information on current and planned activities on Federal efforts related to tissue engineering.²²

¹⁹ See http://tissueengineering.gov/advancing_tissue_science_&_engineering.pdf.

²⁰ <http://www.wtec.org/SCE/>.

²¹ http://www.nist.gov/bdd/biomaterials/functional_imaging_regenerative_medicine_workshop.cfm.

²² <http://tissueengineering.gov>.

i. How does NIH coordinate its research policies on regenerative medicine among the various institutes?

Answer: NIH coordinates research policies as well as funding priorities, information, and goals for regenerative medicine across the NIH Institutes and Centers (ICs), as well as across Federal agencies, through a variety of means, including standing committees and working groups and via symposiums, workshops, and the issuance of funding opportunity announcements (FOAs). Three standing groups are: (1) MATES IWG (described above); (2) the NIH Stem Cell Implementation Committee; and (3) the NIH Center for Regenerative Medicine (NIH CRM). The ICs primarily supporting regenerative medicine and cell-based therapy research are: National Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Biomedical Imaging and Bioengineering (NIBIB), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Environmental Health Sciences (NIEHS), National Institute of General Medical Sciences (NIGMS), and National Institute of Neurological Disorders and Stroke (NINDS).

MATES IWG is the means by which individual NIH ICs and Federal agencies involved in tissue engineering and regenerative medicine stay informed of each other's activities and coordinate efforts in a timely and efficient manner. MATES IWG is currently chaired by NIBIB, one of the 27 ICs that make up the NIH.

NIH coordinates stem cell research (a component of regenerative medicine research) through NIH's long-standing stem cell implementation committee. Comprised of many NIH ICs, the stem cell implementation committee provides a forum to respond rapidly to requests for information, implement training on and compliance with emerging changes in Federal and NIH policy, and jointly develop NIH funding opportunity announcements related to stem cell research.

In response to the rapid developments in stem cell research, and the potential for cell-based therapies, NIH leadership, through the NIH Common Fund, established the NIH Center for Regenerative Medicine (CRM) and hired its first director in 2011. The NIH CRM serves as a resource to intramural and extramural investigators across all of the NIH ICs to address issues concerning the translation of basic stem cell science into cell-based therapies, and focuses on issues of broad relevance.²³

These three independent but related groups allow the NIH to efficiently and effectively respond to new developments in both the discovery science and practical application of regenerative medicine at the level of the individual ICs as well as trans-NIH environments.

ii. How does NIH set research priorities and goals across institutes for regenerative medicine?

Answer: Many ICs are active in various aspects of regenerative medicine. The IC extramural program and intramural research staff have frequent interactions through the various committees described here, and at scientific conferences at NIH and elsewhere, which stimulates scientific discussion and informs the priority setting at NIH.

In addition, the recently established NIH CRM is providing a coordinating focus for research across ICs. The NIH CRM is a community resource that works to provide the infrastructure to support and accelerate the clinical translation of stem cell-based technologies, and to develop widely available resources to be used as standards in stem cell research and regenerative medicine. For a variety of patient populations,

²³ More information on the NIH CRM and its activities is available at <http://crm.nih.gov/default.asp>.

the Center facilitates generation of induced non-embryonic pluripotent stem cells, as well as the derivation or isolation of other types of stem cells. The NIH CRM also provides funds to intramural investigators to pilot projects on clinical applications of induced pluripotent stem cells.²⁴ In addition to NIH CRM, and as discussed above, the MATES IWG facilitates inter-agency coordination through its activities and implementation of the strategic plan.

iii. How does NIH coordinate research projects on regenerative medicine with FDA, Department of Defense and other federal agencies?

Answer: The NIH coordinates research on regenerative medicine with other Federal agencies primarily through MATES IWG (participants listed above), by jointly sponsoring workshops and scientific symposia, and jointly participating in funding initiatives. The MATES IWG is open to all Federal agencies that have interests or activities related to tissue science and engineering. The coordinated effort helps its members (including NIH) to identify research gaps, emerging areas of research, and funding opportunities. Most recently, through the MATES IGW, four NIH ICs (NIBIB, NHLBI, NIDCR, and NIAMS), NSF, and NIST co-sponsored a workshop on Functional Imaging for Regenerative Medicine. Held on May 31 – June 1, 2012, at NIST, the workshop identified areas of opportunity, and stimulated new collaborations and applications of cutting edge imaging methods in tissue engineering and regenerative medicine.

In addition, NIH continues to collaborate with the United States military by contributing intellectual input as well as funding to the Armed Forces Institute for Regenerative Medicine (AFIRM).²⁵ Also, NIH helped address the problem of immune rejection strategies and provided other key input used to craft the solicitation for the second phase of AFIRM.

NIH and FDA are collaborating on a series of unique workshops that aim to move pluripotent (non-embryonic) stem cell products into the clinic. The first meeting, “Pluripotent Stem Cells in Translation: Early Decisions” took place in March 2011. The second meeting, “Pluripotent Stem Cells in Translation: Preclinical Considerations” will be held on the NIH campus in July 2012. Industry, academic and clinical scientists as well as staff from FDA and NIH are expected to participate. The NIH and FDA are actively planning for the next joint workshop, which will focus on clinical research. Also, several NIH ICs have established Memorandums of Understanding (MOUs) with FDA for specific regenerative medicine projects. FDA and NIH also serve on various joint committees to discuss emerging issues, protocols, and concerns related to the translation of research findings into improved public health.

To further coordination efforts, ad hoc working groups have been created at the request of the NIH Director. A recent example is the novel effort by the Defense Advanced Research Projects Agency (DARPA), FDA, and NIH on “Microphysiological Systems” in which human tissues will be engineered and integrated on *in vitro* platforms to mimic human tissue responses to drug challenge. Further details on this effort are described below.

iv. How does NIH work with FDA on regulatory science initiatives identified as important to advancing product development and approval of regenerative medicine?

Answer: NIH and FDA funded four programs under the Regulatory Science Initiative as part of the NIH Common Fund. As a result of this collaboration, a new Heart-Lung Micromachine is being developed. The Heart-Lung Micromachine is an *in vitro* mimic of the human heart and lung. It is an example of a

²⁴ A listing of projects supported by the NIH Common Fund that relate to regenerative medicine/tissue engineering is available at <http://commonfund.nih.gov/stemcells/fundedresearch.aspx>.

²⁵ Information on this collaboration is available at <http://www.afirm.mil/>.

“microphysiological system” or “tissue chip” that could be used for drug development. The program has been expanded in FY 2012 and includes collaboration between NIH, DARPA, and FDA to develop and integrate tissue chips for ten different human systems.²⁶

Also, the American Institute of Medical and Biological Engineering (AIMBE) and NIH (with NIBIB as the lead) are co-sponsoring a series of workshops aimed specifically at the “Qualification and Validation of In Vitro Tools and Models for the Pre-clinical Drug Discovery Process” such as the microphysiological systems being developed in the Regulatory Science initiatives described above. The goal is to provide an open forum with grantees and other tool developers to discuss guidelines for validating new tools and models to ensure that these novel systems move rapidly into use in the drug development pathway.

v. How does NIH allow for public input into research prioritization in regenerative medicine?

Answer: NIH employs a number of mechanisms to consult with stakeholders to identify and prioritize research strategies. Examples include posting Requests for Information (RFI) in the NIH Guide for Grants and Contracts and hosting workshops and scientific meetings in advance of drafting funding opportunity announcements in an effort to encourage input from the broader research community, advocacy groups, and the public. For example, on December 11, 2011, NIH issued an RFI announcing that the NIH and FDA were organizing a series of workshops to engage the broader research community regarding requirements necessary for translation of pluripotent stem cell-derived products into the clinic. Additionally, the NIH CRM issued an RFI soliciting public input from the stem cell research community to help direct efforts toward the most efficient and effective ways to address important issues. Scientific priorities are also identified through workshops and scientific symposia. In June 2011, NICHD sponsored a workshop entitled *Stem Cells, Human Reproduction, and Regenerative Medicine*. The workshop was co-sponsored with the American Academy for Reproductive Medicine and the Society of Gynecologic Investigation. In October 2011, NHLBI sponsored a Symposium on Cardiovascular Regenerative Medicine, which brought together experts in basic stem cell biology, as well as clinical cardiovascular medicine, to discuss emerging basic science, preclinical animal models, and their potential for clinical application.

In addition, the NIH ICs each have Advisory Councils, composed of scientific and public members chosen for their expertise related to the research mission of each IC, who provide guidance on research priorities. The NIH CRM has two advisory boards, the first is comprised of NIH scientists, and the second is comprised of external representatives. External council members are selected to provide, in aggregate, the breadth and depth of extramural expertise that will be critical as NIH CRM moves toward translational therapies. The Council meets in person at least once annually.

NIH also has a website for obtaining public input on an ongoing basis.²⁷

Question 2: It is my understanding that there is no dedicated funding for the Geroscience Interest Group (GIG), but that the work of the group could have potential benefits to each of its 20 member institutes and centers. Are there plans for future partnerships among the GIG members to use traditional mechanisms of funding support available at the NIH (PA's, RFA's, the Common Fund, etc.) to advance specific areas of research more efficiently? If so, can you describe how such collaboration might work?

Answer: The NIH Geroscience Interest Group (GSIG) was formed to accelerate and coordinate efforts to promote further discoveries on the common risks and mechanisms behind age-related diseases and

²⁶ More information on the Regulatory Science Initiatives is at <http://commonfund.nih.gov/regulatoryscience/>.

²⁷ <http://feedback.nih.gov/>.

conditions by developing a collaborative framework that includes multiple NIH Institutes. By pooling resources and expertise, the GSIG identifies major cross-cutting areas of research and proposes coordinated approaches to identify hurdles and envision solutions.

In addition to conducting cross-institute informational activities such as seminars and other activities, one of the GSIG's principal goals is to develop trans-NIH initiatives, including Program Announcements (PAs), Request for Applications (RFAs), and other suitable mechanisms. The model initially being used to achieve these collaborations is identification of relevant topics through discussion by the Executive Committee, followed by prioritization and organization of workshops to canvass the researchers in the outside community. If the workshop leads to positive feedback, then an RFA (or other mechanism) will be developed by a lead IC with assistance from members from other ICs interested in the topic as a way of gaining further input from the research community, a large-scale workshop tentatively entitled "Geroscience: Foundations for Delaying Chronic Disease and Increasing Healthspan" is planned for fall 2013. Another approach involves expansion of current IC RFAs to incorporate aims related to aging and health. For example, the scope of an ongoing RFA from NIAID on regeneration of the thymus -- an organ whose function decreases dramatically with aging, likely leading to a decrease in immune response -- will be expanded to solicit applications for studies related to immune function in older individuals. A Common Fund initiative, while a possibility in the future, is not currently under discussion.

Question 3: Given the anticipated increasing health needs of our rapidly aging population, do you envision additional institutional support for the GSIG in the form of a coordinating committee or a "Blueprint" as its members identify major cross-cutting areas of research to pursue and aim to translate research findings into interventions to delay or prevent chronic disease?

Answer: The GSIG is a very recent development within the NIH, having started activities less than a year ago. As such, the momentum is very strong, with solid support and commitment from NIH leadership to this new venture. Considering the wide range of diseases and disabilities that have their roots in the aging process, coupled with recent advances in our understanding of aging biology, it is conceivable that future investments in this venture will be considered.

Question 4. Dr. Collins. The issue of NIH's policy to deny funding for Parthenogenetic stem cell lines is something that troubles me. As you know, these lines would not require the donation of additional oocytes, thereby obviating any health and bioethical concerns. It seems to me that there could be great potential in this research, and removing restrictions on federal funds for existing Parthenogenetic lines, already derived, may help expedite treatments for millions of patients living with many of our most devastating diseases. I ask that you please explain to me why NIH has denied federal funding for this research and what steps NIH may or may not be taking in the future to address this issue.

Answer: As you may know, NIH issued the *NIH Guidelines for Human Stem Cell Research* (the Guidelines) in response to an Executive Order issued by President Obama in 2009. The NIH Guidelines reflect a careful consideration of the wide range of public perspectives gathered through a public comment process. The Guidelines focus on the ethical requirements to ensure informed, voluntary consent for the donation of embryos remaining after *in vitro fertilization* (IVF) treatment by a couple or an individual who sought such treatment. They prohibit NIH funding for research using human embryonic stem cells (hESCs) from other sources, including somatic cell nuclear transfer (SCNT), parthenogenesis, and embryos created for research purposes.

NIH decided to exclude parthenogenesis as a source of stem cells because it raises complex ethical issues. In particular, there are health risks to women who choose to undergo the procedures involved in oocyte

donation, including risks associated with hormonal treatments needed to induce oocyte production (see National Academies, *Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research: Workshop Report*.²⁸ In addition to the health issues, there are additional considerations that would need to be addressed at the time the oocytes are obtained. For a couple undergoing IVF, oocyte donation could reduce their chances of achieving success. For a woman undergoing oocyte retrieval for the sole purpose of donating oocytes to research, the risks and benefits would be different.

While NIH is committed to reviewing the Guidelines periodically, as appropriate, any reconsideration of the decision to exclude parthenogenesis would need to address these complex issues and consider public perspectives and concerns.

Question 5: The NIH Guidelines on Human Stem Cell Research suggest that the "NIH shall review and update these guidelines periodically, as appropriate." It has now been nearly three years since the effective date of the Guidelines. When will the NIH either update its guidelines to reflect technological advances related to stem cells, including parthenogenesis, or issue new guidance? Please provide this Committee with a specific date for when such a process will commence.

Answer: NIH is committed to reviewing the *NIH Guidelines for Human Stem Cell Research* (the Guidelines) periodically, as appropriate.

²⁸ http://www.nap.edu/catalog.php?record_id=11832.

The Honorable Leonard Lance

Question 1. Would you agree that we would benefit from clearer coordination of critical care research? What can be done to ensure greater coordination among the various disciplines? Is NIH an appropriate place to centralize that coordination?

Answer: We agree that more coordination is needed and that NIH can play a role in critical care research. In December 2011, NIH approved the establishment of Office of Emergency Care Research (OECR) to serve as the primary focal point and chief coordinating component for research and research training in the emergency setting. The Office will interface with the multidisciplinary extramural research community, coordinate relevant efforts across NIH, and communicate with other Federal agencies as appropriate. The placement of OECR within the National Institute of General Medical Sciences (NIGMS), the NIH's 'basic research' institute, provides a home where trans-NIH and multidisciplinary efforts are already supported. For instance, the U. S. Critical Illness and Injury Trials Group was supported primarily by NIGMS with input from several other Institutes and Centers with the goal of helping the multiple disciplines responsible for critical care come together to better plan and carry out pertinent research.

The newly established OECR within NIGMS will be a venue for research in the early stages of critical illness that present through the emergency department. The new OECR will cut across the missions of Institutes and Centers to facilitate and promote synergy in research and research training in the emergency setting; foster communication and interactions related to emergency medicine efforts across HHS and other Federal agencies; hold annual meetings to identify new research and research training opportunities in the emergency setting; and serve as liaison with professional societies and patient advocacy groups involved in emergency care medicine.

Question 2. Pulmonary Fibrosis currently has no known cure. After hearing from experts in the field, it is my understanding that part of the reason is because there is not enough information on the cause and progression of the disease. Is there any reason why, within the existing organic authority granted to NIH by the Congress, that you and your staff could not

- i. **increase funding for pulmonary fibrosis research, and**
- ii. **take the critical first step in the eventual creation of a national pulmonary fibrosis patient surveillance registry by creating a National Pulmonary Fibrosis Advisory Board to advise the NIH (and Congress) on the necessary elements in such a future registry that would accelerate the search for a treatment and someday, a cure, for pulmonary fibrosis?**

Answer: Supporting research in pulmonary fibrosis (PF) has long been a high priority of the National Heart, Lung, and Blood Institute (NHLBI), and we have taken steps within our authority to advance the field. Funding for PF research increased from \$10.4 million and \$14.2 million in FYs 2004-2005 to \$23.5 million and \$28.4 million in FYs 2010-2011, reflecting a substantial growth in PF-related research projects ranging from investigation of basic cellular mechanisms to evaluation of promising new treatments. The number of NHLBI-funded PF program project grants, which support multiple investigators working synergistically on closely related research projects, will double in 2012. Support for PF research has also increased via broader NHLBI pulmonary research initiatives, including the Centers for Advanced Diagnostics and Therapeutics (CADET), Phase II Clinical Trials of Novel Therapeutics, and Translational Program Project Grants. NHLBI staff collaborates frequently with scientific and patient organization communities in planning and promoting PF research activities. In March 2012, the NHLBI participated in the first Fibrosis Across Organ Systems symposium, sponsored by the American Thoracic Society and the Keystone Fibrosis Symposium, at which cutting-edge advances and research needs in PF

were discussed and prioritized. In late 2012, the Institute will convene scientific and medical experts at a program planning workshop in PF to identify promising and timely opportunities for advancing future research and accelerating progress.

In light of ongoing collaborations with the PF research community and patient advocacy groups, and the upcoming workshop, NHLBI does not think that a National Pulmonary Fibrosis Advisory Board is a necessary step at this time. NHLBI has ongoing discussions with academic researchers, scientific/medical societies, and patient advocacy groups on the infrastructures needed to accelerate PF research. In March and June 2012, NHLBI staff met with Pulmonary Fibrosis Foundation representatives and academic researchers to discuss their plans for establishing a national registry for PF and a bio-repository. The broad consensus from that meeting is the academic researchers and Pulmonary Fibrosis Foundation will move forward with their plan to establish a PF patient registry. NHLBI will continue its support for the PF bio-repository as an integral part of NHLBI-sponsored Lung Tissue Research Consortium. The PF registry is on track with plans to initially utilize several academic medical centers that are part of the NHLBI IPF Clinical Research Network (IPFnet) because of these centers' experience in accurately diagnosing and their track record of recruiting PF patients.

Question 3. I recently read a June 2011 article that you wrote in Nature Reviews entitled Mining for Therapeutic Gold. I found it to be a great piece about the need to research new uses of abandoned drugs. I was intrigued that you mentioned the need for “incentives for further development and commercialization” and the importance of intellectual property considerations. Would you please elaborate on the challenges that intellectual property considerations present?

Answer: Through a new partnership with a number of pharmaceutical companies, NIH established a new program to facilitate collaborative efforts between industry and academic investigators to support research on new indications for drugs. To help bring the parties together, the program developed template agreements to help streamline the legal and administrative process for partnering across multiple organizations. The agreements are designed to save time and effort as well as provide a roadmap for handling intellectual property used in or developed through the program. The NIH is also developing a comprehensive database of approved and investigational drugs (the NCATS Pharmaceutical Collection) and working with FDA to advance opportunities in this promising area. These efforts are a crucial component of the NIH effort to decrease the time, cost, and attrition rate involved in bringing promising new therapies to the public.

Repositioning drugs that have not been FDA approved (drug rescue) and drugs that are already approved (drug repurposing) requires consideration of many factors including, but not limited to technical and research hurdles, market opportunities, production costs, patient medical needs, and regulatory approvals. It is also important to consider the intellectual property and any patent rights on the ability to develop and market a rescued or repurposed drug successfully. Successful drug rescue or repurposing is estimated to take an additional 5-10 years of development after the original drug was abandoned.

Some of the intellectual property challenges and considerations in drug rescue and repurposing are:

- Whether sufficient time remains on the life of the drug's patents for the company to recoup its expenses after taking on considerable research and financial risks to repurpose its drug.
- Whether additional research and clinical trials for the rescued or repurposed drug lead to new intellectual property.
- Whether any necessary collaboration with another organization can be conducted under terms that are mutually agreeable.

Question 4. There are numerous conditions that lack therapies, such as Alzheimer's or Parkinson's disease. Part of the reason is these conditions progress slowly over many years, and new treatments require lengthy research and clinical trials. These longer clinical trials are often not feasible because there is little if any patent protection left after approval of the drug. As a result many companies have stopped all of their research in particular areas such as treatments for mental health disorders, chronic disease prevention, and neurological conditions. Are there ways to overcome the intellectual property protection barrier to facilitate the development of new treatments for these conditions?

Answer: The National Institutes of Health (NIH) also recognizes that the lengthy clinical trial process can present barriers in the development of new treatments. Several avenues exist for making inroads into the lengthy research and clinical trial process and associated intellectual property issues. First, if the drug development process is shortened, there would be a longer period of intellectual property protection for the marketed drug or device. Accordingly, the Clinical Translational Science Awards (CTSA) program of the National Center for Advancing Translational Sciences (NCATS) is fostering ways to enhance the conduct of clinical research by improving efficiency, for instance, by streamlining and shortening Institutional Review Board review for clinical studies while continuing to protect patients' interests, and clinical trial contracting time. Second, NIH – in a targeted NCATS initiative called Discovering New Therapeutic Uses for Existing Molecules is working to reduce hurdles and time delays related to developing, negotiating and implementing appropriate legal agreements among multiple parties (pharma, government, academia) in repurposing drugs; it is doing so, in part, by pre-negotiating template agreements concerning intellectual property and data rights for use with certain NIH grant award programs. This is being done in the new NIH-Industry pilot program entitled, "Discovering New Therapeutic Uses for Existing Molecules."²⁹

In addition, public-private-partnerships (PPPs) that encourage the sharing of data, research and other responsibilities associated with validating novel targets and compounds can be a powerful means of bringing together the appropriate experts, resources, and incentives for all parties. Policies and rules that encourage PPPs can facilitate this approach.

Question 5. As a leader of the Human Genome Project, you know better than anyone the potential benefit that personalized medicine can deliver for patients. Increasing the number of diagnostic tests that can predict which medicines work for which patients would go a long way to improve patient care. Unfortunately, I am hearing from patient advocates that they are concerned that the field is not progressing as quickly as they would like. Can you talk about ways that you think we encourage faster development of personalized medicine?

Answer: The investment in the Human Genome Project (HGP) is beginning to deliver returns to the Nation, although fully realizing the gains in the clinic will take some time just as it has in other domains of medicine. Current estimates are that it takes at least 17 years for a scientific discovery to translate from the research lab into routine clinical care. However, HGP-empowered diagnostics and therapeutics already are being employed to personalize an individual's clinical care. For example:

- Genetic testing is now used as the standard of care to guide HIV treatment with abacavir (Ziagen)—a drug that dramatically improves survival, but can be deadly for some patients;
- Widespread use of genetic and genomic diagnostics to guide treatment for breast and ovarian cancer;
- Use of genetic tests to target therapies to patients who will benefit from specific therapeutics, such as vemurafenib (Zelboraf®) for melanoma and ivacaftor (Kalydeco™) for cystic fibrosis;

²⁹ <http://grants.nih.gov/grants/guide/pa-files/PA-12-203.html>.

- Whole genome sequencing to diagnose rare and otherwise undiagnosed diseases, including, the NIH Undiagnosed Diseases Program, which recently discovered two previously unknown diseases and the case of Alexis and Noah Beery, the California twins referred to in my testimony before the Senate Appropriations Subcommittee on Labor, HHS, and Education on March 28, 2012.³⁰

Additionally, exciting research programs at NIH are underway to push the limits of our knowledge about how to apply genomics to clinical care:

- The National Human Genome Research Institute's (NHGRI) Clinical Sequencing Exploratory Research program supports multi-disciplinary projects that bring together clinicians, bioinformaticians, and ethicists to research the challenges of utilizing genomic sequence data in the clinic in the routine practice of medicine.
- The National Cancer Institute (NCI) makes available a suite of analysis tools—called CellMiner—to help researchers compare patterns of drug activity and gene expression to identify drugs that could be effective against different forms of cancer. For example, researchers found that an investigational drug being tested for colon cancer might also be effective against melanoma.
- The NIH Pharmacogenomics Research Network is a network of research groups focused on understanding how genes affect responses to medicines. Remarkable advances in this field have identified DNA variations that contribute to adverse drug reactions or may render drugs completely ineffective for certain people. Pharmacogenomic information is now included in about 10 percent of labels for drugs approved by FDA to treat a range of conditions, including HIV/AIDS, cancer, seizures, and cardiovascular disorders.
- A study initiated with Federal stimulus funding provided by NIH, and continued with funding from the Harvard Stem Cell Institute, showed that certain drugs could reverse signs of Parkinson's disease in cultured cells with certain genetic mutations. The findings suggest that patients with Parkinson's disease could be screened for particular genetic variations and then be treated with drugs that are effective in those genetic backgrounds.

Question 6. I would like to commend you for your Discovering New Therapeutics for Existing Molecules. It is a great example of the government and private sector working together to meet a common goal. Can you please talk a little bit about this initiative? I realize it wasn't introduced very long ago, but if you have any progress you can share, I'd love to hear it. Finally, I'd like to know if you have identified any barriers that would keep this initiative from being as successful as possible.

Answer: On May 3, 2012, HHS Secretary Kathleen Sebelius and NIH Director Dr. Francis Collins held a press conference to announce the launch of the Discovering New Therapeutic Uses for Existing Molecules initiative. The NIH will partner with industry and academia in a unique manner that incentivizes all parties, streamlines administrative and legal processes, and tips the scales for research success by only using compounds that already have been shown to have a reasonable safety profile for use in humans. This NIH-industry collaboration will match researchers with 58 compounds to test ideas for new therapeutic uses. Since the launch of the program, the total number of compounds the companies are making available has more than doubled. Since this is a pilot program, NCATS will be carefully assessing any barriers to progress and developing remedies to those barriers as the program evolves.

At the time of the press conference, NIH had established a partnership with three pharmaceutical companies. After the press conference, five additional pharmaceutical companies joined the program. The eight partners are: Abbott, AstraZeneca, Bristol-Myers Squibb Company, Eli Lilly and Company,

³⁰ http://www.nih.gov/about/director/budgetrequest/fy2013_collins_senate.pdf.

GlaxoSmithKline, Janssen Pharmaceutical Research & Development, L.L.C., Pfizer, and Sanofi. Collectively, the eight partners are making 58 compounds available for this initiative. The areas of medicine for which the compounds were originally being developed were broad, including cancer, immune system, respiratory system, nervous system, and others.

The funding opportunity announcements for this pilot initiative were released on June 12, 2012, and a technical assistance webinar for potential applicants is planned for June 25, 2012. There has already been a strong interest from the scientific community. Approximately 6-8 awards, totaling up to \$20 million, are expected to be made around June 2013.

Question 7. Dr. Collins, we've seen the five-year relative survival rate for all cancers jump from roughly 50 percent to 67 percent since the passage of the National Cancer Act in 1971. Yet pancreatic cancer survival rates have remained in the single digits and largely unchanged. There are still no early detection tools or effective treatments for this disease. Why has progress been so slow and what are the specific challenges we face in fighting this type of cancer?

Answer: While significant strides have been made towards understanding pancreatic cancer in the past two decades, significant challenges remain. This is due, in part, to the aggressive nature of the vast majority of pancreatic cancers, the complex biology of this cancer, the lack of early screening tools, and the absence of effective targeted therapeutic agents. Pancreatic cancer is distinct from most other cancers because the tumor elicits a shell-like biological barrier around itself, limiting blood flow and making it difficult to deliver drugs to the tumor. In addition, because symptoms often do not arise until there is extensive disease, approximately half of pancreatic cancer patients are diagnosed at a late stage when the disease is inoperable or has already spread to other organs. Although the outlook is somewhat better for patients who are diagnosed with early disease, it still proves fatal to the vast majority of them.

One aspect of the predominant form of pancreatic cancer might seem to be advantageous: over 90 percent harbor similar or identical mutations in the same gene, the K-RAS gene; moreover these mutations in K-RAS also occur frequently in tumors in other organs, including the lung and colon. However, despite more than two decades of intense work by the pharmaceutical industry and the academic sector, efforts to block the effects of these mutations in the fashion achieved with other gene-targeted drugs, such as Gleevec or Herceptin, have been uniformly unsuccessful. Furthermore, the large number of additional genetic mutations involved in pancreatic cancer further complicates the development of effective targeted therapies to disable the growth of cancer cells and arrest progression of the disease.

Despite these difficulties, and thanks to improved technologies and the interest of many outstanding investigators in pancreatic cancer, the National Cancer Institute (NCI) has dramatically increased the number of grants to fund meritorious research in this area. Some of this effort is focused specifically on pancreatic cancer. This includes a broad spectrum of research, from improving the detection and management of this cancer to the development of relevant cell-based and animal models that enable a detailed study of the pathogenesis of this cancer and the preclinical testing of new candidate therapeutic interventions.

In light of these distinct scientific challenges, NCI completed a comprehensive action plan for pancreatic cancer research in September 2011 that identified future opportunities with the highest likelihood for improving survival rates, including the identification of genetic factors, environmental exposures, and gene-environment interactions that contribute to the development of this cancer. Much of these research efforts are underway and yielding valuable information. Further, NCI-supported scientists are studying a primary challenge in treating pancreatic cancer – the presence of mutations in the K-RAS gene, which has been considered the genetic driver of pancreatic cancer initiation and progression for more than 30 years.

In 2012, NCI-supported researchers demonstrated that inhibition of an enzyme known as protein kinase C delta (PKCD) is toxic to pancreatic cancer cells. Since the PKCD enzyme is tumor-promoting in the presence of mutant K-RAS, it is possible that a small molecule inhibitor of PKCD could have potential as a targeted therapy for pancreatic tumors, and other cancers with K-RAS mutations. While this particular study focused on pancreatic cancer cells, the researchers, based at the Boston University Cancer Center, are also exploring the basic molecular and cellular biology of various cancer types. NCI-supported research will continue to build upon these findings in an effort to determine whether PKCD inhibitors have clinical applications for pancreatic and other cancers.

The keys to progress clearly lie in further identification of risk factors and genetic changes, greater knowledge of the metastatic process, and better methods of early detection and treatment. Continued research on these areas is a high priority for NCI and NIH. Specific efforts include funding extensive genomic analyses through NCI's Cancer Genome Atlas (TCGA) with high quality biospecimens (including those obtained via rapid autopsy). TCGA is currently sequencing over 60 cases of pancreatic cancer that have come through the pipeline, and will soon provide a comprehensive picture of the pancreatic adenocarcinoma genome. Other efforts include development of novel mechanisms such as chemical attacks and nanotechnology delivery systems to breach the shell-like barrier around pancreatic cancer, and imaging and biomarker research to improve detection.

Question 8. Dr. Collins, I'm struck by the comparison that could be made between the tools we currently have available to fight pancreatic cancer and what we had available to fight HIV/AIDS in the early 1980s. We have made considerable progress in HIV/AIDS and it is now considered a manageable disease instead of a deadly disease. What lessons can we learn from the programs that were put in place for AIDS research that can be applied to pancreatic cancer?

Answer: Most advances in HIV/AIDS treatment have depended on at least six factors. 1) Identification of the infectious cause (HIV) of this disease. 2) Development of a sensitive and specific blood test to identify infected individuals. 3) Development of relevant cell-based and animal models. 4) Identification of key viral activities whose inhibition interfered with virus replication and reduced disease in preclinical models. 5) Identification of practical drugs that inhibited one of these viral activities much more efficiently than they inhibited related cell-encoded activities. 6) Multidrug treatment to reduce the development of drug resistance in treated individuals. Some cell-encoded activities, such as the main receptor by which the virus binds to cells, were also validated as targets for therapeutic intervention. However, the vast majority of FDA-approved drugs are directed against viral activities, rather than against cell-encoded activities, as it is easier to develop interventions against activities of the foreign infectious agent than interventions against cell-encoded targets. Moreover, the most important viral targets are enzymes---proteins whose functions are most readily blocked by small chemicals that often become approved and effective drugs. In looking for possible relevant lessons for pancreatic cancer, there is no strong evidence that pancreatic cancer is caused by an oncogenic infectious agent, thus interventions against this disease need to be directed against cell-encoded activities, which is a greater challenge. However, the need to determine the utility of a sensitive diagnostic blood test, the development of relevant cell-based and animal models, identification, and validation of key cell-based activities, development of inhibitors and their preclinical testing, and the ultimate goal of multidrug chemotherapy have similarities to HIV/AIDS, and many other diseases. In fact, much of NCI-supported research in this area is modeled along these lines.

Question 9. Do you currently have a long-term and comprehensive plan to strategically address pancreatic cancer?

Answer: In 2008, the NCI Gastrointestinal Steering Committee convened a "Clinical Trials Planning Meeting on Pancreas Cancer Treatment," to discuss the integration of basic and clinical knowledge in the

design of clinical trials in pancreatic ductal adenocarcinoma (PDAC). A Consensus Report from this meeting was published in the *Journal of Clinical Oncology* in November 2009.³¹ The committee placed major emphasis on three areas: enhancement of research to identify and validate the relevant targets and molecular pathways in PDAC, cancer stem cells, and the microenvironment. The committee also identified additional research priorities, including the development of combination therapies and predictive biomarkers. The Consensus Report has helped to guide many of NCI's pancreatic cancer research efforts over the past three years.

Nevertheless, it is important to observe that, while we can plan ways to study pancreatic cancer with many methods at our disposal, our understanding of the disease is not yet mature enough to develop a plan for prevention, early diagnosis, and treatment. Consistent with NIH's experience, for advances on important clinical aspects of the disease, it is important to encourage investigators to propose imaginative and technically sophisticated approaches and to fund those that are judged to have strong scientific merit. It is customary for NCI leadership, investigators in our research communities, and scientific program managers to periodically review progress toward critical goals and to "scan the horizon" for methods and ideas that could be employed to nurture future efforts. NCI is using its established Clinical and Translational Advisory Committee to oversee such reviews and "horizon scans" for several cancers, including pancreatic cancer, that have proven refractory to improvements in prevention, early detection, and treatment. The subcommittees being formed to conduct these surveys will include subject experts, Cancer Center directors, and other well-established investigators in cancer research. The intent of these exercises will be to determine whether NCI has been employing the full range of its talents and methodologies to study such cancers, whether significant progress has occurred, and how the Institute can be more effective in pursuit of the goal of reducing the morbidity and mortality of every type of cancer.

Question 10. Dr. Collins, in the NCI's "Action Plan for FY 2011", the NCI noted that there should be a specific program announcement call for grants focused on pancreatic cancer. While I was heartened by that, I found out later that no such announcement was ever made. Can you tell me why NCI didn't follow through with its own recommendation? Can we expect to see one in the near future?

Answer: In the National Cancer Institute's (NCI) "Action Plan for FY 2011" regarding pancreatic cancer research, the development of a Program Announcement (PA) for Research Project (R01) grants focused on pancreatic cancer is cited as a potential new initiative. NCI is continuing to explore the possibility of developing a PA for R01 grants focused on pancreatic cancer. A PA is a formal statement about a new or ongoing extramural activity or program, and is seen as a signal of an Institute's interest in the field with the goal of stimulating applications. As we have considered a potential PA, we also have noted the entry of outstanding investigators into the field and the large and growing number of applications we now receive for studies of pancreatic cancer. The increased interest in this field and corresponding increase in high-quality research applications has resulted in an increase in NCI funding for pancreatic cancer research over time. For example, research funding coded specifically for pancreatic cancer at NCI in FY 2012 was \$105 million, a 44 percent increase over FY 2007. Moreover, we continue to accept Exploratory/Developmental Research (R21) and Small Grant (R03) applications through Pilot Studies in Pancreatic Cancer (PA-11-297 and PA-11-298). These PAs were issued in August 2011, are active through January 2015, and have the potential to generate highly innovative findings or technical/methodological improvements that could have a major impact on the field of pancreatic cancer research.

Given the challenges that encompass pancreatic cancer and the need for a better overall understanding of the disease in which to build future research upon, NCI must give careful consideration to the

³¹ <http://jco.ascopubs.org/content/27/33/5660.full.pdf>.

development and issuance of a PA for R01 grants focused on pancreatic cancer. Our continued discussions regarding the development of this potential PA are necessary to ensure scientific opportunity and the greatest potential for reward, and we will be carefully considering all of the recommendations made by the Clinical Trials and Translational Research Advisory Committee Pancreatic Cancer Working Group.

Question 11. With respect to pancreatic cancer, we have made some strides toward understanding the basic biology of the disease in the last decade, such as understanding some of the complexities of the disease. For example, we now understand that pancreatic cancer tumors differ from most other tumor types, making it one of the most challenging cancers to research. But the translation of these findings to patient benefit is still long-term and underscores the need for a focused effort in pancreatic cancer. What are your specific plans for translating these discoveries into clinical care and improving the dismal survival rates for pancreatic cancer?

Answer: The National Cancer Institute (NCI) continues to support a diverse pancreatic cancer research portfolio, including research focused on the translation of basic findings to clinical applications. Examples of specific NCI-supported initiatives already underway include research in the following areas:

- **Preclinical Models:** Recent research, building upon NCI investments in preclinical models of pancreatic cancer, indicates that instillation of an enzyme called PEGPH20 can increase delivery of the chemotherapy gemcitabine to mouse pancreatic tumors. This approach resulted in a significant increase in survival time. An early-phase clinical trial, led by an investigator at the Fred Hutchinson Cancer Research Center, an NCI-designated Center, is underway to test the combination of PEGPH20 and gemcitabine in people with metastatic pancreatic cancer.
- **Clinical Trials:** NCI is currently supporting 62 active pancreatic cancer clinical trials, including a 950-patient trial – the largest of its kind – to evaluate the benefit of adding a targeted drug and/or radiation therapy to combination chemotherapy. NCI is also supporting immunotherapy research for advanced pancreatic cancer, including a trial of the targeted drug ipilimumab and another to study the effect of tumor-infiltrating lymphocytes, which are isolated white blood cells from surgically removed pancreatic cancer metastases, and can be mobilized to work against the tumor.
- **Targeted Therapies:** In 2012, NCI-supported researchers demonstrated that inhibition of an enzyme known as protein kinase C delta (PKCD) is toxic to pancreatic cancer cells. Since the PKCD enzyme is tumor-promoting in the presence of mutant K-RAS, it is possible that a small molecule inhibitor of PKCD could have potential as a targeted therapy for pancreatic tumors, and other cancers with K-RAS mutations. While this particular study focused on pancreatic cancer cells, the researchers, based at the Boston University Cancer Center, are also exploring the basic molecular and cellular biology of various cancer types. NCI-supported research will continue to build upon these findings in an effort to determine whether PKCD inhibitors have clinical applications for pancreatic and other cancers.
- **Combination Therapy:** NCI-supported research also includes analysis of the recent findings that losartan, a drug commonly used to treat hypertension, has been shown to “open” compressed tumor vessels and make dense pancreatic cancer cells more permeable to anti-cancer drugs. Efforts are under way to test whether adding losartan to standard therapy can improve survival.

Question 12. Does the NIH consider clinical need when they prioritize grants for funding?

Answer: Yes. Clinical need or public health burden is considered by NIH in prioritizing grant funding. For research priority setting, a major factor in measuring burden is to identify trends and not just to rank different conditions by their current burden. Is there an emerging problem? Will it grow in the future?

Has there been any progress in preventing a disease or managing a condition? For some diseases, measures of incidence or prevalence are relatively accessible. For other diseases and conditions, measures, such as death rates or hospitalizations, provide more accessible indicators of trends in disease burden.

There are sometimes variations in NIH Research and Development spending per incident or prevalent case or per any metric for disease specific burden. These variations have several explanations. First, even simple measures of burden such as incidence and prevalence are obtained from multiple sources (different Federal offices and published scholarly studies). They are not measured consistently across diseases. Second, available measures do not capture all dimensions of burden. Third, NIH has a special mandate to focus on rare diseases and other areas that lack the market potential to attract private sector interest. Fourth, and most importantly, NIH sets priorities based on both burden of illness and our collective assessment of how best to reduce the burden associated with specific diseases—through the identification of knowledge gaps which must be overcome, as well as determining how best to capitalize on scientific opportunities.

Research and the NIH priority setting process are inherently dynamic. They develop and adjust to new opportunities. The distribution of funding for any year is but a snapshot of an evolving process. The relationship between scientific opportunities, burden of illness, and disease-specific funding is multifaceted and not always straightforward or linear.

The amount of NIH funding identified with a particular disease is not a complete indication of the attention paid to that condition. Disease-specific funding alone does not reflect the likely benefits of basic research or research coded to other conditions. New scientific opportunities often flow from NIH-sponsored research on broad scientific themes (such as genome projects, development of instrumentation, training in clinical research, or developments in basic science). Historically, support of these themes has often yielded insights and capacity to stimulate research to address specific diseases and often several different diseases.

Question 13. According to NCI's funding data, in FY 2011 the Institute funded 353 researchers to study pancreatic cancer, which has a 6% survival rate. By comparison, NCI awarded grants to over 1,400 researchers to study breast cancer, which has a 90% five year relative survival rate, and 827 researchers to study prostate cancer, which has a 100% five year relative survival rate. Shouldn't we be focusing at least as much attention on pancreatic cancer research as we do on cancers with much higher survival rates?

Answer: Public health burden, including factors such as disease incidence and mortality, is always a consideration for allocating National Cancer Institute (NCI) funding. It is one of many factors considered when allocating funds from the NIH and NCI budgets; other factors include scientific opportunities and the quality of the research proposals we receive. Determining public health needs requires a complex evaluation of many aspects of disease, taking into consideration trends, not just data from a single year.

NIH and NCI set priorities based on both burden of illness and our collective assessment of how best to reduce the burden associated with specific diseases; these include the identification of topics on which our knowledge is deficient, as well as a determination of how best to capitalize on scientific opportunities for making progress.

It is customary for NCI leadership, investigators in our research communities, and scientific program managers to periodically review progress toward critical goals, and to “scan the horizon” for methods and ideas that could be employed to nurture future efforts. NCI is using its established Clinical and Translational Advisory Committee to oversee such reviews and “horizon scans” for several cancers,

including pancreatic cancer, that have proven refractory to improvements in prevention, early detection, and treatment. The subcommittees being formed to conduct these surveys will include subject experts, Cancer Center directors, and other well-established investigators in cancer research. The intent of these exercises will be to determine whether NCI has been employing the full range of its talents and methodologies to study such cancers, whether significant progress has occurred, and how the Institute can be more effective in pursuit of the goal of reducing the morbidity and mortality of every type of cancer.

Question 14. Dr. Collins, I am particularly interested in what we are doing to encourage junior investigators to enter the field of pancreatic cancer. Do you have any plans for attracting more young investigators to pancreatic cancer research so that we can build the field?

Answer: A well-trained and dedicated workforce is needed to conduct pancreatic cancer research across the cancer care continuum. The workforce should include basic, translational, and clinical researchers as well as scientists capable of developing the tools and technologies needed to advance pancreatic cancer research. NCI recognizes the importance of supporting young investigators to ensure that this research progress is sustained. Since the majority of training activities occur in the context of research conducted in NCI-supported laboratories, the large increase in pancreatic cancer research in the NCI portfolio means that many more trainees are getting direct or indirect exposure to the skills and goals of such research.

In addition, NCI funds training using a number of mechanisms and provides support for trainees at a variety of career stages, including predoctoral students, postdoctoral fellows, early-career independent investigators, and newly trained clinicians. The NCI intramural program also provides support for trainees.

Trainees supported by NCI engage in research on a broad range of topics. Many grantees are investigating the biology of pancreatic cancer, including the signaling pathways and other cellular factors that contribute to pancreatic cancer onset and progression. Epidemiological research is being conducted on risk factors, including genetic factors associated with pancreatic cancer, with one study focusing on the epidemiology of young-onset pancreatic cancer. Training projects are also investigating potential biomarkers for detection of pancreatic cancer. In addition, there are studies focused on the underutilization of surgical resection of pancreatic tumors and the influence of genetic factors on patient response to gemcitabine, a drug that is part of the standard chemotherapeutic regimen for pancreatic cancer.

NCI remains committed to training the next generation of investigators interested in pursuing pancreatic cancer research. The continued support of these young scientists is a critical component of NCI's overall investment in advancing the progress in this important research area.

Question 15. As I understand the science, pancreatic tumors do not create their own blood supply the way other types of cancer do. We also know that pancreatic cancer tumors are surrounded by thick tissue. All of this makes it more difficult to get drugs to the tumor. Is it fair to say that finding answers to this difficult challenge will lead to breakthroughs in other cancers?

Answer: As your question suggests, pancreatic cancer is distinct from other cancers due to a shell-like biologic barrier that the tumor builds around itself. This barrier causes increased fluid pressure within the tumor microenvironment that compresses existing blood vessels and prevents new blood vessels from forming, thereby limiting the blood supply to the tumor. Consequently, when a chemotherapy drug is administered, the restricted blood flow prevents sufficient amounts of the drug from reaching the tumor.

Although the precise mechanisms that cause this restricted blood flow in the pancreatic tumor are not fully understood, NCI-supported mouse model research is proving to be an invaluable tool in the search

for answers to this question as well as in devising new therapeutic options for patients. Scientists found that administering an experimental drug that inhibits a signaling pathway linked to several cancers (known as the “Hedgehog pathway”) disrupted the barrier and expanded blood vessels in the tumor, allowing for increased delivery of gemcitabine chemotherapy. Hedgehog inhibitors have since been tested in clinical trials of pancreatic cancer, with mixed results, but researchers are investigating whether different approaches may be effective. Recent research indicates a drug called PEGPH20 can also increase delivery of gemcitabine chemotherapy to mouse pancreatic tumors. The result was a significant increase in survival time in mice treated with gemcitabine plus PEGPH20 compared with mice treated with gemcitabine alone. An early-phase clinical trial is under way to test the combination in people with metastatic pancreatic cancer.

NCI-supported research also includes analysis of the recent findings that losartan, a drug commonly used to treat hypertension, has been shown to “open” compressed tumor vessels and make dense pancreatic cancer cells more permeable to anti-cancer drugs. Efforts are underway to test whether adding losartan to standard therapy can improve survival.

As your question suggests, critical research exploring the biological properties of one cancer often leads to breakthroughs on other cancers. Delivery of drugs to other tumor types is sometimes compromised, although by different biologic mechanisms. Discovery of means to improve drug delivery to pancreatic cancers may benefit treatment of other tumor types, just as it is possible that discoveries regarding drug delivery to other tumor types may lead to advances for pancreatic cancer.

The Honorable Bill Cassidy

Question 1: Studies have shown the need for specific research with regards to emergency care. NIH recognized that need and announced in January a new office of Emergency Care Research. To date, nothing has happened in regards to establishing that new office. Could the NIH give an update as to the progress, if any, of establishing an Emergency Care Research office?

Answer: On December 5, 2011, NIH approved the organizational establishment of the new, trans-NIH Office of Emergency Care Research (OECR) housed within the National Institute of General Medical Sciences (NIGMS). Prior to the OECR's approval, NIH established the OECR Steering Committee, which is composed of Directors from NIGMS, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Heart, Lung, and Blood Institute, the National Institute of Neurological Disorders and Stroke, and the National Institute of Nursing Research. The Committee will provide oversight and guidance to OECR. The Office will serve as the primary focal point and chief coordinating component for research and research training in the emergency setting for NIH, interfacing with the multidisciplinary extramural research communities, coordinating relevant efforts across NIH, and communicate with other Federal agencies as appropriate. In addition, the new NIH Working Group on Emergency Care Research, composed of representatives from most NIH Institutes and Centers, has begun meeting and will work in concert with OECR.

While the recruitment of a permanent director is underway, Dr. Walter J. Koroshetz, M.D., currently serves as the OECR Acting Director. These developments position NIH to move forward with its mission of advancing, coordinating, and providing information about basic, clinical, and translational biomedical research and research training within the emergency care setting necessary for improvement in the diagnoses and treatment of patients.

Question 2. Research has shown that funding for disease research is not matched by the actual burden of disease in the United States by the NIH. The NIH is currently not funding disease related research proportionally to the cost and burden of disease. The NIH states that scientific opportunity is a major criterion for distribution of funding that might trump burden of disease and disease related funding. Is it not true that scientific opportunity is created in part by where funding is directed?

Answer: NIH employs a priority setting process that strikes a dynamic balance between public health needs and scientific opportunity. Thanks to the rapid pace of discovery today, scientific opportunities occur at unprecedented speed. Simultaneously, public health needs may shift rapidly, whether due to a newly emerging threat or a newly discovered strategy that ameliorates need. In order to strike an appropriate balance between the two, NIH has created a process that involves several levels of expert review which essentially functions as a competitive market for ideas to inform decision making.

The level of funding associated with a specific disease or condition reflects the collective judgment of multiple experts with regard to the promise of various research opportunities and the best way to capitalize on those opportunities to address public health needs. These include: the individual investigators and teams of investigators as they develop proposals; scientists who serve on peer review study groups to review and score proposals based on their professional assessments; Institute and Centers (IC) program officers who bring expertise and seek consultation to their assessment of gaps and opportunities in a particular disease area or field of investigation; and members of IC advisory groups who provide a secondary review of research proposals and provide recommendations to IC directors regarding funding of grants and balancing the overall IC portfolio across multiple disease areas and fields of investigation.

Scientific opportunities often arise in areas of research that are not necessarily disease focused, but rather focused on basic biological *processes* and behavioral functioning. For example, our knowledge of genomics and the availability of DNA-based drugs (*e.g.*, Macugen to treat age-related macular degeneration) in the clinic all stem from fundamental research conducted in the 1950s on the structure of DNA. By understanding basic mechanisms of functioning, such projects lead to knowledge that can be applied to understanding how such functioning may go awry in multiple diseases and disorders, and to better intervening against them.

Furthermore, it is important to note that research directed towards any one disease or condition may inform not only strategies to ameliorate the burden of that particular disease or condition, but also may impact efforts to intervene for a number of other diseases. A potent example of this was the discovery through the NIH Undiagnosed Diseases Program in the NIH Clinical Center of an entirely new genetic condition in which a pair of sisters suffered from joint pain and mysterious calcification of the arteries in their extremities. The cause of this previously unknown condition was found to be blockage of an undiscovered enzyme pathway in their arteries. This dramatic new understanding of how large arteries maintain their normal health resulted in immediate and significant new research directions in both basic and clinical arenas, leading to insights that may impact treatment and prevention strategies for any number of diseases.

Because it is not always possible to predict how scientific findings, both basic and applied, may inform efforts to devise new means to ameliorate disease burden, NIH has devised a dynamic and expert-driven approach towards determining its funding priorities. This process ensures an ever-increasing understanding of basic biological functioning and the continued application of that understanding to the amelioration of disease burden.

With regard to the question whether scientific opportunity is created in part by where funding is directed, we agree that funding is certainly required to capitalize on existing scientific opportunities and to create new ones. Constraining R&D funding to target a few, selected diseases, or to be in proportion to some incomplete measure of burden, might still advance science. But it would do so more slowly than would an unconstrained approach to capitalizing on new opportunities regardless of which disease a proposed investigation might address or whether the investigation is focused on more basic, non-disease-specific research. Also, as outlined above, a balanced portfolio across multiple fields of investigation is vital to assure advance in the effort to reduce disease burden.

Question 3. Research done from 1996-2006 has shown that the variant between disease funding and disease impact on mortality, disability and costs has declined from 39% to 33% over that ten year span. The NIH website, in regard to this type of data, is hard to navigate and extrapolate the statistics; could the NIH please tell the Subcommittee if these percentages have gotten better in recent years? Does the NIH have available the absolute funds that were redirected along with the variant percentage between disease funding and disease burden? Also, how often do the NIH Institute Center National Advisory Councils redirect funds, if so how much of these funds and grants have been redirected? If the funding and grants have not been redirected, why hasn't the NIH addressed the disproportionate distribution of grants among disease research?

Answer: The question appears to refer to the findings in a recent article by Gillum et al.³² That article, in turn, is a follow-up to work by Gross et al.³³ Gillum et al. find that for 29 conditions, the burden of

³² Gillum LA, Gouveia C, Dorsey ER, Pletcher M, Mathers CD, McCulloch CE, Johnston SC. (2011) NIH Disease Funding Levels and Burden of Disease. PLoS ONE 6(2): e16837. doi:10.1371/journal.pone.0016837. <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0016837>.

disease as measured by Disability Adjusted Life Years (DALYs) accounted for 39 percent of the variation in NIH funding of disease specific research in 1996 but only 33 percent of the variation in 2006. They report that an Institute of Medicine (IOM) committee “recommended greater consideration of disease burden.” Readers are left to conclude that the modest and declining correlation is necessarily a bad thing. We disagree with that conclusion.

In 1998, an IOM committee recommended that “In setting priorities, NIH should strengthen its analysis and use of health data, such as burdens and costs of diseases, and of data on the impact of research on the health of the public.”³⁴ It did not recommend that NIH allocate research in proportion to some measure of burden. In fact it cautioned that, “It should be kept in mind, however, that there is no simple metric for the use of these data, and the relationship between such data and allocations of research funding will not be simple because health problems are not equally ripe for research advances.”

Many factors must be considered in the allocation of funds from the NIH budget, including public health needs, scientific opportunities, and the quality of research proposals. All these factors are weighed in NIH’s dynamic and expert-driven approach towards determining funding priorities.

Consequently, we would argue against the conclusion that a slight drop in the percentage of variation explained by levels of burden is inherently bad and requires correction. We cannot tell the committee at this time whether the correlation has changed in recent years, as the analysis has not been performed with updated estimates of DALYs from the World Health Organization.

The analysis by Gillum does, perhaps inadvertently, indicate the difficulty with attempts to measure disease-specific burden and advocating its use as a determinant of R&D funding. Two of the conditions identified as receiving more than expected funding are AIDS and diabetes. AIDS remains a major killer worldwide. As an infectious disease, it includes the threat of drug resistance or otherwise evolving and leading to a pandemic. However the burden estimate used in the analysis of DALYs attributed to AIDS in North America fails to capture the worldwide public health burden and the dynamic risk associated with a major communicable disease. Likewise, diabetes is an underlying risk factor for heart disease and several other conditions. We doubt that the DALY estimate for diabetes captures the indirect burden of diabetes. Also, the trends indicate an increase in the prevalence of diabetes over time, another burden indicator not captured in a static, annual estimate of DALYs.

As to the questions about redirection of funds, the NIH Institute and Center (IC) National Advisory Councils do not redirect funds. They provide recommendations to the ICs about funding. Re-direction of funding often is a result of an IC publishing its priorities and encouraging applications that meet its priorities – thus the pool of applications is re-directed. In addition, ICs will take into account such priorities when making funding decisions between different projects of equal scientific merit. Thus, it would not be possible to develop an NIH report that shows “redirection.”

Question 4. If the percentage of variance between disease funding and disease burden has grown worse or minimally improved since 2006, does the NIH believe that external oversight into the NIH funding would affect these numbers? Overall, is it possible that the effectiveness of the NIH and the way it directs funds could perhaps be improved by external oversight that is less prone to internal politics and maintaining the status quo and which would give a different perspective on how funding would impact different programs?

³³ Gross CP, Anderson GF, Powe NR (1999) The relation between funding by the National Institutes of Health and the burden of disease. *N Engl J Med* 340:1881–1887.

³⁴ Institute of Medicine (1998) Scientific opportunities and public needs: Improving priority setting and public input at the NIH. National Institutes of Health Priority Setting Committee, Institute of Medicine. National Academy Press, <http://www.nap.edu>.

Answer: We do not believe that advances in science which lead to progress in reducing overall health burden would benefit from additional constraints on the allocation of funding to be proportional to a measure of disease burden determined by an external overseer. As outlined in the response to question 2 we believe the broadly inclusive, expert-driven NIH priority setting process provides an efficient and equitable means to allocate R&D funds. It provides the most promising system to identify and capitalize on existing opportunities, to address knowledge gaps, to develop new insights and tools, and, ultimately, to advance progress to reduce health burden. We believe that providing an open market for ideas by encouraging investigator initiated proposals and using scientific peer review, the NIH priority system is more insulated from “internal politics and maintaining the status quo” than it would be by a top-down, directed system.

The formulation of the question suggests the external oversight group would adopt disease burden as the primary criterion for allocation of research funding to NIH. If measures of disease burden are decoupled from evaluation of scientific opportunity and other criteria for allocation of R&D funding, it increases the likelihood that the oversight group will be subject to considerable political pressure.

We believe that any external oversight group would find it extremely challenging to develop objective, comprehensive, and comparable measures of burden for the thousands of diseases afflicting United States residents and addressed by the R&D portfolio. It would need to find a way to combine into a single index for each disease or condition the burden of life years lost to premature mortality with the burden of living with a debilitating and painful condition, the economic cost of treatment and any additional adverse impacts on family members and the community. As well as the current level of burden, the oversight group must consider whether the burden of a specific condition is likely to increase or recede as the demographic mix of the population changes over time and as health-related behaviors evolve. Evaluation of the dynamic risk of burden includes consideration of the threat that a communicable or infectious disease with little or no current health impact today could evolve into a devastating pandemic.

Numerous arguments could be made for why the standard metric for evaluating disease burden understates the adverse impact of any particular condition. Differences among methodologies for calculating burden may lead to controversy, and will also make it difficult to compare across disease categories (*e.g.*, diabetes as an underlying cause of heart disease and organ failure, the adverse impact of mental illness or addiction on children of victims and on public safety).

Question 5. NIH has funded certain studies that do not appear to be an appropriate use of federal funding, especially when funding is strained due to the economic times and when other diseases have a greater burden both medically and fiscally. These studies (ex. Homosexual male sex practices, underage Chinese prostitution disease occurrence, etc.) have been funded with a substantial amount of the disease funding within the NIH budget (over millions of dollars). The amount that the NIH has given for HIV/AIDS research, does that number include these studies? If so, how much of NIH expenditures are for the study of basic, translational applied research in these studies?

Answer: The global AIDS epidemic represents the major public health challenge of our generation. Despite considerable progress, the HIV/AIDS epidemic continues to expand. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in 2010, more than 34 million people were living with HIV/AIDS; 2.7 million were newly infected; and 1.8 million people died of AIDS-related illnesses. In the United States, the CDC estimates that more than 1.2 million people are HIV-infected; and someone is infected with HIV every nine and a half minutes. AIDS in the United States disproportionately affects men who have sex with men, racial and ethnic populations, women of color, and young adults.

The FY 2011 budget for the trans-NIH AIDS research program was \$3.06 billion. This amount includes the total trans-NIH support for intramural and extramural research for basic, clinical, behavioral, social science, and translational research on HIV/AIDS and the wide spectrum of AIDS-associated malignancies, opportunistic infections, co-infections, and clinical complications; as well as research management support; research centers; and training. Approximately 50 percent of the total NIH AIDS research budget supports basic research on HIV focused on the transmission, acquisition, establishment, and maintenance of HIV infection and the causes of its associated profound immune deficiency and severe clinical complications. Findings from these studies provide the critical building blocks and foundation for the discovery, development, and clinical testing of new and better drugs, treatment regimens, and prevention interventions, including an HIV vaccine and microbicides, that are applicable to all populations at risk including women, adolescents, men who have sex with men, substance users, and racial and ethnic populations in the United States.

Approximately \$412 million of the total AIDS budget is devoted to behavioral and social science research. NIH supports research to better understand the risk behaviors and social contexts that lead to HIV infection and disease progression, how to change those behavioral and social contexts, and how to maintain protective behaviors once they are adopted. Studies are developing and evaluating interventions directly targeted to substance abuse and sexual behaviors associated with HIV transmission. NIH invested approximately \$278 million in epidemiology studies, including studies of transmission of HIV and disease progression. These studies are investigating the risk factors associated with HIV transmission and acquisition in various populations in the United States and worldwide in order to develop unique, targeted prevention strategies that take into account ethnic and cultural differences, and the risk factors that resulted in HIV acquisition among different subpopulations.

Understanding the epidemic and preventing HIV in communities with the greatest prevalence of infection also prevents the spread of infection beyond those populations. This research is critical to slowing the further spread of the AIDS epidemic, increasing the uptake of voluntary HIV counseling and testing in at risk populations, and linking HIV-infected individuals to treatment and care. Studies conducted among high risk populations have also provided critical information about individuals who are highly exposed to HIV yet remain uninfected and about individuals who are exposed to HIV yet control the infection without treatment, known as “elite controllers.” The research findings in these high-risk populations are providing valuable information that is essential to the development of vaccines, microbicides, and other biomedical prevention strategies as well as to the development of new treatment strategies and eventually a cure.

Question 6. Various publishers in the scientific and medical field are concerned with issues concerning the NIH’s PubMed Central and have requested the following questions. The NIH has noted the success of the NIH’s PubMed Central for making current research and medical articles accessible to the public. However, some of the articles distributed by PubMed [Central] are by private publishing companies. Does the NIH have the percentage of articles that are distributed by PubMed [Central] by publishers? Also, what steps have the NIH taken to monitor and minimize users from circumventing restrictions that stop illegal downloads of published articles? Does the NIH keep track of those copyright infringements and do they alert the publisher of those articles that have been attempted to be bulk downloaded?

Answer: The purpose of PubMed Central (PMC) is to provide a freely-accessible, permanent archive of published biomedical literature. PMC currently contains more than 2.4 million articles which have been published in scientific journals. All content made available on PubMed Central has been voluntarily provided with the permission of the copyright holder, either the publisher or the author.

While many of the articles in PMC are the result of NIH-funded research, almost 1,100 journals voluntarily deposit all of their articles into PMC on a regular basis, regardless of whether the articles report work that is NIH-funded. Close to 2,000 other journals deposit selected articles. NIH takes copyright very seriously and takes active steps to ensure that deposited works are not compromised in any way. All articles in PMC include the publisher's original copyright statement as well as a link to a PMC copyright notice that informs users of applicable restrictions and responsibilities. PMC uses automated methods similar to those used by publishers to recognize bulk downloading activity and immediately blocks such users.

Question 7. The America COMPETES Act of 2007 required the NIH's sister agency NSF to make project outcome records available to the public on-line, and DoE is working with publishers to make research reports available to the public on-line, including a reference to the funding source and a link to any published journal article reporting on that research. Why hasn't NIH made research reports publically available on-line, given they are available much sooner than any published article reporting on the research?

Answer: Within days of making an award, NIH publically posts the title, abstract, and public health relevance sections of all research grants through the NIH RePORT website.³⁵ Grantees are instructed to include a reference to the funding source when issuing any publication, and publications are similarly referenced on the NIH RePORT web site in association with specific grant awards. NIH annual progress reports and closeout reports are not intended to disseminate scientific results and are not a substitute for peer-reviewed journal articles. NIH annual progress and closeout reports are treated as confidential because they may contain information that awardees consider proprietary. Progress reports also may contain information about specific challenges being faced while conducting the research and the plans investigators are undertaking to overcome such challenges, as well as information about budget and resource use.

Peer-reviewed journal articles are the preferred mechanism for disseminating high-quality scientific research. Progress reports are not peer-reviewed. Reliance on peer-reviewed papers as the primary means of dissemination also limits the administrative burden NIH places on awardees by avoiding the need for additional, duplicative dissemination documents.

The NIH is the only Federal agency that has a legislatively mandated public access policy and it has been in place for over five years. The NIH Public Access Policy ensures that the public has access to the peer-reviewed papers resulting from NIH-funded research by making these papers available without charge on PubMed Central. It puts quality research in the hands of scientists in industry and academia to accelerate the pace of discovery, and increases the accountability to the American public. It also helps create a central repository of biomedical information, PubMed Central, which serves multiple audiences from researchers to students, and from doctors to entrepreneurs.

Question 8. The NIH relies heavily on peer review. Does the NIH have any data showing that this system of review is actually reproducible? Would two independent review groups make the same funding decisions on a series of grants? Is there any information to support that funded grants with high scores have a greater impact than funded grants that have lower scores?

Answer: NIH is deeply committed to the integrity of the peer review system. A multi-level process is used for assigning each grant application to the initial review group that best matches in terms of science and expertise and avoids conflicts of interest.

³⁵ <http://report.nih.gov>.

NIH has not conducted systematic studies of the reproducibility of reviewers' opinions in the context of its own review process. However, NIH is considering a number of new experiments in peer review, as suggested by the recent report from the Advisory Committee to the Director (Dr. Collins) that met June 14, 2012.³⁶ Testing the reproducibility of the peer review results is among the possibilities to explore.

NIH is not in a position to fund applications that have low scores from peer review. Therefore, little reliable information exists to answer the question concerning relative impact of applications with high versus low scores given that nearly all funded applications score in the high range.

³⁶ <http://acd.od.nih.gov/Diversity%20in%20the%20Biomedical%20Research%20Workforce%20Report.pdf>.

The Honorable Lois Capps

Question 1. Despite the difficulties in bringing basic research to fruition, we have made great strides for a variety of rare diseases such as spinal muscular atrophy, the number one genetic killer of children under the age of two. As a result, a number of potential therapies are either already in limited clinical trials or will be ready to commence with phase 1 trials in the next 12-24 months. However, the challenge for diseases like SMA is infrastructure—especially to operate effective clinical trials networks. I am pleased to be working with my colleagues to develop bipartisan legislation to help address this need through the establishment of pediatric research consortia with an enhanced focus on rare diseases and clinical trials for those diseases. Dr. Collins, can you please talk about how the NIH is working to fill this particular need for clinical resources, and specific steps that can be taken to more deeply engage the Institutes in the clinical investment required to find treatments for rare pediatric diseases like SMA?

Answer: Candidate therapeutics are emerging for several pediatric neurological disorders, including SMA, because of translational programs supported by NIH, foundations, and industry that build on basic research advances. Clinical trials infrastructure is certainly essential to move these potential treatments into early phase clinical testing. NIH has anticipated this growing need and has new and continuing programs in place to address it.

For SMA and other neurological disorders, NINDS established the new NeuroNEXT clinical trials network, with central data and coordinating centers and 25 clinical sites throughout the United States. NeuroNEXT has selected a study of SMA biomarkers as the first clinical study in the network.

NeuroNEXT was specifically designed to improve early phase clinical trials for children with neurological disorders by including children's hospitals, as well as centers with adult and pediatric services. Because NeuroNEXT serves multiple diseases, the network can engage more extensive resources and expertise than could be dedicated to a single disease. To enhance the speed and efficiency of trials, NeuroNEXT addresses regulatory and contract issues, clinical trials design, and patient recruitment. The network protects intellectual property to encourage testing of the best candidates from the NIH, academia, foundations, or industry. NINDS has solicited proposals for clinical trials from all of these sources, and review of proposals is now underway. Following a joint NIH-FDA scientific workshop on SMA biomarkers in May 2011 that engaged the SMA research and patient community, and a subsequent solicitation, NeuroNEXT has selected a study of SMA biomarkers as the first clinical study in the network. Biomarkers of disease progression or therapeutic action are key measures that will expedite testing of therapeutic candidates.

With regard to pediatric research more generally, virtually all NIH Institutes and Centers invest in pediatric research – more than \$3 billion last year in total. Several NIH programs bring together research teams and infrastructure for clinical research on pediatric diseases, including rare diseases. A number of Clinical and Translational Science Award (CTSA) sites, for example, have a strong emphasis on pediatric research. A CTSA Pediatrics Steering Committee enhances coordination across the centers, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has led several workshops over the years on pediatric issues relevant to the CTSA program. The NIH Rare Diseases Clinical Research Network, led by the Office of Rare Diseases Research within the National Center for advancing Translational Sciences, also supports pediatric relevant centers, in cooperation with NINDS, NICHD, and other Institutes as appropriate. Since the program began in 2003, 21 of the 24 supported Consortia have had clinical protocols that enrolled pediatric patients, including more than 60 natural history or interventional studies performed at more than 200 research institutions in the US and abroad. In addition to its role in these programs, NICHD supports nearly 60 research networks on various aspects of children's health and development or pediatric conditions. Among these are the Collaborative

Pediatric Critical Care Network, the Global Network for Women's and Children's Health Research, and the Neonatal Research Network. Each of these takes advantage of scientific expertise that may be widely dispersed across the country. Among other notable NIH programs, the Global Rare Diseases Patient Registry Data Repository, currently under construction, will allow patient registries to deposit deidentified data for research, and the Undiagnosed Diseases Program, which began on the Bethesda campus, is now expanding as a Common Fund program with extramural sites that will enhance access for undiagnosed pediatric patients.

Question 2. Last September the CDC issued updated "Guidelines for Reducing Transmission of HIV, Hepatitis B, and Hepatitis C through Solid Organ Transplantation." As part of the guidelines, the agency identified areas recommended for further research, including the need for research on the risk-benefit of transplanting organs from HIV-infected donors into HIV-infected recipients. However, currently law blocks the Organ Procurement and Transplantation Network from any organ donation from HIV-positive individuals—even for research.

Dr. Collins, could you please comment on the areas of research which NIH might explore or fund if this ban on the use of HIV-infected organs for transplantation in HIV-positive patients were lifted?

Answer: The use of widely available highly-active antiretroviral therapy (HAART) has transformed HIV infection into a well-controlled chronic disease. Associated with long-term survival is the appearance of a population of HIV-infected individuals with end-stage kidney or liver failure that may be due to the same causes as are found in the general population, but may also be related directly to HIV infection (*i.e.*, HIV nephropathy) or to co-infection with hepatitis B or hepatitis C viruses. Such individuals currently receive kidney or liver transplants with organs from HIV-negative donors. A recently completed NIH-sponsored study of kidney transplantation in HIV-infected recipients demonstrated acceptable transplant outcomes, albeit with a higher-than-expected incidence of treatable kidney rejection. However, outcomes in liver recipients co-infected with HIV and hepatitis C virus were not as consistently successful as liver transplantation in recipients not infected with hepatitis C virus. New and more effective drugs for the treatment of hepatitis C may improve outcomes in co-infected recipients.

Little is known about the transplantation of donor organs from HIV-positive individuals into HIV-positive recipients, as the use of such organs is currently prohibited by law in the United States. Absent this policy, research questions NIH might consider would include the following areas:

- Clinical outcomes of HIV-positive to HIV-positive organ transplants, including patient survival, graft survival, rejection rates and complications, with accessory studies of the immunologic mechanisms and optimal characteristics for HIV-positive donor organs and HIV-positive recipients underlying these outcomes
- The immune response to transplantation in the setting of HIV infection and comorbidities
- Development of improved treatment regimens for the treatment of HIV-positive transplant recipients with or without co-infection with hepatitis B or hepatitis C viruses
- Drug interactions and health outcomes resulting from concomitant use of HAART, hepatitis treatments, if applicable, and transplant immunosuppression
- Development and optimization of rapid screening of donor organs to avoid introducing a resistant HIV strain in the transplant recipient
- The response to the introduction, through the transplanted organ, of a new strain of HIV to an HIV-infected individual

QUESTIONS RAISED DURING THE HEARING

The Honorable John Dingell (excerpt from transcript)

DINGELL:

Good morning, Doctor.

I'd like to begin by asking this question. Would you please submit for the record information regarding the proposed merger of NIDA and NIAAA? And I would hope that you would give us the premises under which the budget neutrality of the combining of these two institutes was established.

COLLINS:

I'd be happy to submit that for the record.

DINGELL:

Thank you, Doctor.

Answer: We will work with the committee to address your concerns.

The Honorable Phil Gingrey (excerpt from transcript)

GINGREY:

Yes. Dr. Collins, thank you for that answer. Of course, we need to see a return on investment for taxpayer's dollars, especially in areas that impact so many Americans and one costly disease that estimates or impact 26 million Americans is diabetes. Medical costs of Americans with diabetes are more than twice those without the disease. So in light of these rather startling but accurate figures, I recently shared my support for the special diabetes program in a letter circulated by my colleagues, representatives Whitfield and DeGette. Can you share with the committee the return on investment of this program and how is this helping Americans burdened by diabetes?

(intervening dialogue)

PITTS:

Yes. Dr. Gingrey has gone out with the patient. So we'll have to -- you'll have to follow up for the record.

COLLINS:

OK. I'd be happy to follow up for the record.

Answer: As you mentioned, type 1 and type 2 diabetes affect an estimated 26 million Americans and the prevalence of both type 1 and type 2 diabetes is growing. In fact, research supported by the Special Diabetes Program estimated that the number of children with type 1 diabetes rose 23 percent between 2001 and 2009. Diabetes also takes an enormous personal economic toll and, in the most recent estimate, costs the Nation an estimated \$174 billion. Research to prevent this disease and to improve the health and quality of life of people with diabetes is critical.

The Special Diabetes Program for Type 1 Diabetes Research augments regularly appropriated funds that the HHS receives for diabetes research. These funds have enabled the creation of unique, innovative, and collaborative research consortia and clinical trials networks that have generated important and beneficial findings for people with type 1 diabetes. As a result of research supported by the Special Diabetes Program, people with type 1 diabetes are living longer and healthier lives. For example, the landmark Diabetes Control and Complications Trial (DCCT) and its long-term follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), supported in part by the Special Diabetes Program, demonstrated that intensive glucose control, beginning as soon as possible after diagnosis, can prevent or delay life-threatening and costly complications of diabetes. These complications of the eyes, kidneys, nerves, and heart are costly to treat, and contribute significantly to the annual cost of diabetes. According to data from DCCT/EDIC, implementation of intensive insulin management in the entire United States type 1 diabetic population (an estimated 1 million) could result in 920,000 years of sight; 691,000 years free from end-stage renal disease; 678,000 years free from amputation; and 611,000 years of life.

Diabetes is the leading cause of kidney failure, requiring dialysis or a kidney transplant for survival. Each year 110,000 patients in the United States start lifesaving treatments for kidney failure that cost \$42.5 billion annually. Recent findings from EDIC demonstrated that controlling blood glucose reduced the long-term risk of developing kidney disease by 50 percent. These findings are revolutionizing management of type 1 diabetes and leading to dramatic health benefits and economic savings.

In light of these important findings, the NIH, through the Special Diabetes Program, has made the development of tools to improve patients' ability to control their blood glucose levels, such as artificial pancreas technology, a high priority. An artificial pancreas would enable easier and more appropriately adjusted delivery of insulin in response to minute-to-minute changes in blood glucose levels. This could improve insulin treatment and care for people with diabetes, helping people to achieve good blood

glucose control and reducing events that lead to costly ambulatory services, emergency room visits, and in-patient hospitalizations. An artificial pancreas could help reduce the economic burden of diabetes in the United States by helping people with diabetes delay or prevent diabetic complications. Trials to develop and test these technologies have been supported by the Special Diabetes Program.

Importantly, research supported by the Special Diabetes Program is far-reaching, benefitting not only people with type 1 diabetes, but also people with type 2 diabetes and people with other autoimmune diseases. People with type 1 or type 2 diabetes benefit from research to understand insulin-producing beta cells and to find ways to preserve and restore beta cell function and research directed at the disease complications that type 1 and type 2 diabetes share. Special Diabetes Program-supported research to uncover the environmental triggers of type 1 diabetes may have even broader applications because it could also uncover triggers of celiac disease, a digestive disorder that shares some of the same risk genes as type 1 diabetes and affects 1 percent of the United States population.

Even greater returns on the investment in the Special Diabetes Program are expected in the coming years as new findings are generated and further improvements in the health and quality of life of people with diabetes are realized.

